FLUID THERAPY IN ANIMALS

EDITED BY: William W. Muir, Deborah C. Silverstein and Dez Hughes
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FLUID THERAPY IN ANIMALS

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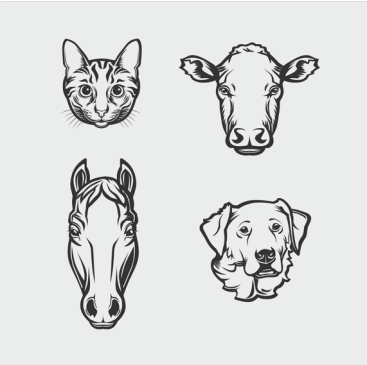

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EDITORIAL
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Editorial: Fluid Therapy in Animals: Physiologic Principles and Contemporary Fluid Resuscitation Considerations

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Editorial on the Research Topic

Fluid Therapy in Animals: Physiologic Principles and Contemporary Fluid Resuscitation Considerations

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INTRODUCTION

What an oversight! Fluids are drugs (1), so why has one of the most administered, and arguably beneficial, therapies employed in veterinary medicine been so inadequately investigated? Intravenous fluids (i.e., drug) can produce positive or negative effects dependent upon their dose and the circumstances (i.e., context) that exist when they are administered (2, 3). Improved understanding of the physiologic principles that determine the effects and consequences of fluid therapy in healthy and diseased animals is essential to good clinical practice (4–86). Notably, most of the "evidence" investigating fluid therapy in animals has been obtained from studies that are not randomized, properly controlled, blinded, adequately powered, or fail to identify predefined primary or secondary outcomes (73, 75, 87, 88). As a result, much of the medical literature provides, "little reliable information on the effectiveness of fluid resuscitation" in diverse clinical scenarios (2, 3, 89–93). Future studies must address these limitations since "fluid therapy might be more difficult than you think" (94), "nothing is more dangerous than conscientious foolishness" (95) and "solely the dose determines that a thing is not a poison" (96). For example, the pharmacokinetics of fluids administered to cats, dogs, horses, or cattle are largely unknown and generally not considered when designing fluid therapy trials although it has been addressed in the human medical literature for more than 20 years (31, 97–100).

This issue of Frontiers in Veterinary Science provides: (1) A review of the terms used to define or describe fluid therapy (Chow); (2) An update on body fluid compartments and the physiological concepts that guide fluid therapy (Stewart; Woodcock and Michel; Smart and Hughes; Cooper and Silverstein); (3) A discussion of fluid kinetics and its relevance to fluid administration in cats (Yiew, Bateman, Hahn, Bersenas, Muir; Yiew, Bateman, Hahn, Bersenas); (4) Contemporary recommendations for the administration of IV fluid regimens in small and large animals (Rudloff and Hopper; Crabtree and Epstein; Adamik and Yozova); (5) The effects of IV fluids on the coagulation system (Boyd et al.); (6) A discussion of fluid administration in animals with naturally occurring disorders and diseases (e.g., food deprivation, dehydration, sepsis, renal, pulmonary, trauma, hemorrhage, traumatic brain injury; Freeman; Dias et al.; Montealegre and Lyons; Constable et al.; Hall and Drobatz; Pigot and Rudloff; Langston and Gordon; Adamantos)

including refractory hypotension (Valverde) and cardiopulmonary resuscitation (Fletcher and Boller); (7) The consequences of fluid overload (Hansen); (8) A description of dynamic fluid therapy monitoring techniques (Boysen and Gommeren); (9) An introduction to fluids of the future (Edwards and Hoareau); and (10) Alternative methods for fluid delivery (Gholami et al.). The information and citations contained within this collection serve as a rich resource for the design of future studies investigating the safety and efficacy of intravenous fluid therapy in animals.

BODY FLUID COMPARTMENTS

Water (i.e., total body water: TBW) is responsible for ∼60–70% of body weight (BW) and is the primary component of all body fluids (101). The two main body fluid compartments are the intracellular fluid (ICF) and extracellular fluid (ECF). Approximately two-thirds (≈40%) of TBW is intracellular fluid (ICF) and one-third (≈20%) extracellular fluid (ECF). The ECF is comprised of four sub-compartments, the intravascular fluid volume (i.e., plasma volume: PV; 4–5% BW), the fluid that surrounds cells (i.e., interstitial fluid volume: IFV; ≈15–18% BW), lymph, and fluids contained within epithelial lined spaces (transcellular fluids) [Stewart; (101–104)]. Severe obesity can increase the relative percentage of the ECF by up to 50% of TBW (≈ 30% BW) (105). The intravascular volume (i.e., blood volume: BV) is comprised of the red cell volume (RBCV; 6–8% BW) and plasma volume (PV) (106, 107). If the packed red blood cell volume (PCV) is known BV can be determined (i.e., BV = PV × 100/100-PCV) (106). Transcellular fluids are infrequently considered when determining water and solute requirements in simple stomached animals but become important in horses and ruminants (108). Determination of the body's fluid compartments is technically challenging, time consuming, and often inaccurate (109–111). Substances used for this purpose (i.e., "dilutional tracer technique") must be non-toxic, easily detectable and sustain a steady state concentration within the compartment (112–114).

Contemporary evidence suggests that the PV is comprised of circulating and non-circulating (15–25% of PV) components, the latter being located within an endothelial surface or glycocalyx layer (GLX) and the channels between vascular epithelial cells (115, 116). The GLX interacts freely with plasma proteins and acts as an surface layer "gatekeeper" for larger molecules selectively reducing plasma solute distribution volume dependent upon their molecular weight (MW), shape (i.e., effective molecular radius), electrical charge, and concentration (11–14, 117). Crystalloids have a shorter intravascular retention time than colloids (100, 118–121).

BLOOD DISTRIBUTION

Blood volume is distributed between the pulmonary (18–20%) and systemic (78–80%) circulations dependent upon their (e.g., brain, heart, lung, and gut) oxygen requirements (VO_2). Veins are ∼30 times more compliant than arteries, contain up to five times more adrenergic receptors than arteries and normally serve as blood reservoirs (122). Some investigators have described the blood volume contained within the systemic veins as either unstressed or stressed (123, 124). The unstressed volume (Vu; ≈70% BV) is equivalent to the blood volume required to fill the veins without increasing the transmural pressure above zero mmHg and the stressed volume (Vs; ≈30% BV) as the volume of blood required to increase the transmural pressure to values above zero (123). Under normal circumstances Vu is believed to serve as a reserve volume that can be mobilized by increasing sympathetic activity (i.e., alpha 1 receptors) thereby increasing vs. (i.e., "effective" BV) (125, 126). The mean circulatory filling pressure (MCFP) is defined as the mean vascular pressure that exists in the systemic circulation after the heart is stopped and is argued to be determinant of venous return and cardiac output (127, 128). A growing number of vascular physiologists however consider this interpretation to be abstract and erroneous opting to believe that cardiac contraction is the independent variable that drives blood flow and determines cardiac output (129–136).

WATER BALANCE

Water balance (i.e., water intake and output) is governed by a variety of neural and neuroendocrine high-gain homeostatic feedback mechanisms that include, osmoreceptors, osmotically stimulated thirst receptors, hormones [e.g., renin-angiotensin-aldosterone system (RAAS), angiotensin-converting enzyme-2 (ACE2)/angiotensin 1–7 (Ang 1–7), vasopressin (antidiuretic hormone: ADH), erythropoietin (EPO), atrial natriuretic peptide (ANP)] and membrane water channels (i.e., aquaporins), especially those located in the renal tubules (137–144). The kidney is responsible for regulating fluid, electrolyte balance and blood volume (145–147). The kidney also produces and secrets erythropoietin (e.g., low Hb, PaO_2, flow) signaling bone marrow to produce more red blood cells. Activated atrial stretch receptors secrete ANP producing vasodilation and increases in glomerular filtration, salt and water excretion, and vascular permeability, thereby regulating PV and lowering arterial blood pressure (ABP) (141, 148). Therefore, the kidney is regarded as a key determinant of both PV and BV. Negatively charged glycosaminoglycans (GAGs) located in the interstitial spaces and lymphatics of the skin also function as non-renal regulators of sodium ion concentration and ECF volume (7, 8) serving as indirect controllers of arterial blood pressure (ABP) by shifting fluid from the interstitial to the intravascular space (7, 8, 149).

BLOOD FLOW AND TISSUE PERFUSION

The heart and vasculature deliver blood to and from the systemic and pulmonary circulations and, in conjunction with interstitial compliance and the lymphatic system, are responsible for ensuring the continuous circulation of fluid throughout the body (5, 5, 150–156). Three categories of capillaries are involved in the

exchange of fluid, gases (O_2, CO_2), and solutes (e.g., albumin) (155, 157). Non-fenestrated or continuous capillaries nourish the tissues of the nervous system, muscle, connective tissue, skin, lung, and fat. Fenestrated (i.e., contain "pores") capillaries perfuse the kidneys, intestinal mucosa, synovial linings, exocrine glands and sinusoidal or discontinuous capillaries with large intercellular breaks (i.e., pores) filter blood in the liver, spleen, and bone marrow (11). All three are coated to a greater or lesser extent by the semi-permeable negatively charged GLX [(11–13); [Yiew, Bateman, Hahn, Bersenas; Rudloff and Hopper; Crabtree and Epstein; Adamik and Yozova; (155, 158)]. Plasma filtration among the different types of capillaries is determined by hydrostatic (mmHg) and osmotic (mOsm/L) pressures, the number and size or their fenestrations [i.e., "pores"]), capillary surface area, the thickness of the GLX, the pre- to postcapillary vascular tone (i.e., resistance ratio), and tissue compliance (3, 159–162). Capillaries in the renal glomeruli are fenestrated (pore: 30–60 nm) but have a smaller effective pore size (pore: ≤15 nm) due to the influence of the GLX on the filtration of larger (>40–50 kDa) molecules (163, 164). Non-fenestrated capillaries (e.g., central nervous system blood brain barrier; ≤1–2 nm) with numerous endothelial transport vesicles enable transcytosis (i.e., transcellular transport of macromolecules). They are less permeable to fluid and electrolyte exchange than fenestrated capillaries, although water and small solutes pass through endothelial intercellular clefts in accordance with hydrostatic pressure differences (157). Non-fenestrated "continuous" capillaries (e.g., skin, lungs, and the blood-brain barrier) have a comparatively small effective pore size (pore: 3–5 nm) that inhibits the trans-vascular flux of fluid and most solutes (160, 163–165).

The GLX constitutes ∼2% of the PV and functions as two layers: a less permeable, dense branch-like inner layer composed of heparin sulfate and glycoproteins and a more permeable porous outer later composed of plasma proteins and glycosaminoglycans (13, 104, 166). The GLX limits albumin (i.e., large molecule) and RBC access, leukocyte contact with the inner layer and endothelial surface (13, 104, 166), participates in cell signaling (i.e., nitric oxide-induced vasorelaxation), provides anti-coagulant effects and protects endothelial cells from oxidative stress (107). Small molecules, such as water, gases, small lipids, and lipid-soluble molecules diffuse freely through the GLX through endothelial intercellular clefts or by facilitated diffusion (158). Larger molecules (i.e., colloids) negligibly penetrate the GLX and distribute in a smaller intravascular volume than crystalloids which readily distribute throughout the entire intravascular space. Recent studies suggest that crystalloid-to-colloid ratios should range from 0.7 to 1.4:1 in contrast to older ratios (i.e., 1:3) (167–175) and that crystalloid-to-blood ratios > 1:1 produce perivascular edema, pulmonary parenchymal stiffness (176), impaired coagulation [Boyd et al.; (177, 178)], increased blood loss (44), and increased vasopressor requirements (43). Disagreements favoring colloids over crystalloids rest more on their delayed diffusion than on their safety [(44, 50–53); Boyd et al.; (179)], risk-benefit ratio (Adamik and Yozova) or cost.

TRANSVASCULAR FLUID FLUX

Traditional Theory

The dynamics of fluid flux (J_v) across capillary walls is historically attributed to Earnest Starling's observations of fluid absorption from connective tissue spaces (Starling 1896) (180). He concluded that capillary hydrostatic pressure was responsible for transudation of a small amount of fluid into the tissues ("frictional resistance of the capillary wall"), thereby forming lymph, and that the colloid osmotic pressure produced by plasma proteins was responsible for fluid absorption. He also postulated that the forces moving fluid in and out of the capillary were almost balanced. Subsequent experiments resulted in mathematical descriptions of Starling's hypothesis and suggested equations wherein J_v (i.e., transvascular fluid flux) is a balance of intravascular capillary (c) intravascular and interstitial (i) hydraulic (i.e., hydrostatic pressure: P) and oncotic [π: colloid osmotic pressure (COP)] forces (Kedem–Katchalski equations) (181). Capillary hydrostatic pressure (P_c) is a function of the hydrostatic P from the inflow (arterial: a) to the outflow (venous: v) end of the capillary and are dependent upon the pre- and post-capillary resistances (R), assuming blood flow remains constant (182–186). A decrease in Ra (e.g., arteriolar vasodilation) or an increase in Rv (venoconstriction) decreases Ra/Rv and increases both P_c and Jv (3). Under normal circumstances Pc is more sensitive to changes in Pv than Pa but during intense arterial vasoconstriction, Pc decreases rapidly (increased Ra/Rv) (3, 185). Plasma proteins are responsible for generating π_c and COP is the hydrostatic pressure required to prevent fluid movement into the plasma or, alternatively, the pressure that pulls fluid across the capillary wall into the plasma. Capillary P_c (i.e., hydraulic push) is therefore opposed by capillary π_c [i.e., osmotic suction: (P_c - π_c)] and Pi is opposed by π_i (Pi - π_i). The Starling hypothesis asserts that fluid is filtered at the arterial end of the capillary because Pc predominates over all other forces, and that fluid is reabsorbed at the venous end of the capillary because π_c (osmotic suction) predominates. Interstitial forces (Pi, π_i) act as modulators of the rate of fluid flux and therefore the volume of Jv (14, 185). Later studies modified Starling's hypothesis to account for transvascular fluid flux rates per unit pressure (i.e., hydraulic conductance: L_p) and the macromolecular sieving properties of the microvascular barrier (Staverman's reflection coefficient: σ) [(12–14); Woodcock and Michel; (173, 187)]. Both L_p and σ vary among different types of capillaries since L_p is dependent upon the number of "pores" and σ is dependent on effective pore diameter. The σ for most plasma solutes ranges from 0 to 1 (i.e., 0 = totally permeable; 1 = totally impermeable) (187). The capillary wall osmotic and σ for water, anions, cations, and smaller soluble substances like glucose is nearly 0 (freely permeable) (160). Larger plasma solutes (>30–40 kDa), like albumin (66–69 kDa; diameter ∼3.5 nm), which accounts for 80% of total plasma protein and commercial semisynthetic colloid solutions (i.e., gelatins, dextran, and hydroxyethyl starches; COP range 24–60 mm Hg) exhibit σ's ranging from 0.7 to 1.0 and are almost impermeant to most the microvascular barrier except the sinusoids of the liver. The incorporation of L_p and σ into Starlings hypothesis is the

basis for what is proclaimed as the "Starling equation" that is still published in most texts [$J_v = L_p$ [$(P_c - P_i) - \sigma (\pi_c - \pi_i)$]], although Starling had little to do with its derivation since the earliest form of the equation did not appear until 1927 (182).

Contemporary Theory

Recent investigations have led to a revision of the Starling hypothesis (165) and the Starling equation based upon GLX COP (π_g): $J_v = L_p$ [$(P_c - P_i) - \sigma (\pi_c - \pi_g)$] [(11); Woodcock and Michel; (188–193)]. It is now realized that the interstitial COP does not directly determine fluid movement across the microvascular wall, and that the effect of π_c on J_v is far less than originally predicted (11, 189–195). The sieving properties of the glycocalyx modify Starling's forces by imposing an obstacle to J_v. The π difference across non-fenestrated capillaries is influenced by the π_g and π_i is far less important in determining Jv than originally proposed. Notably, π_g is negligible compared to π_c such that the osmotic pressure gradient across the glycocalyx is close to π_c rather than the difference between π_c and π_i. Fluid that is filtered through the glycocalyx flows rapidly through narrow inter-endothelial cell breaks, thereby limiting interstitial protein back diffusion into the sub-glycocalyx space. The "Revised" Starling equation [(11); Woodcock and Michel; (189)] has proven to be more consistent with experimental and clinical observations and suggests that (1) J_v is far less than originally predicted; (2) Fluid is not normally reabsorbed from the venous end of the capillary during normal physiologic conditions (steady state no-reabsorption rule); (3) Tissue lymph drainage is the primary route for return of interstitial fluid to the circulation; (4) Interstitial fluid is reabsorbed from the interstitium when P_c decreases until a new steady state is established (14); and (5) Crystalloid is almost as effective as a colloid (Col) administration for treating hypovolemia from blood loss (11, 173–176). These revisions highlight the importance of GLX composition and integrity and the number of inter-endothelial cellular "breaks" (i.e., glycocalyx-junction-break model) in determining the effectiveness of fluid resuscitation (195). They do not negate the "importance of transcapillary refill" as suggested by some (196), but do have important implications regarding fluid selection, rate, and volume for improving fluid efficiency and effectiveness in diseased animals [Woodcock and Michel; (189, 194, 197)].

VOLUME KINETICS

Volume kinetics (VK) determines the volume into which an administered fluid is distributed (i.e., volume of distribution: V_d), the volume of plasma that is completely cleared of the administered fluid per unit time (i.e., clearance: Cl) and the time it takes for the total amount of administered fluid to be reduced by one-half of its original volume (i.e., half-life: $t_{1/2}$) (31). Intravenous fluids are initially distributed into a central compartment (V_c) followed by diffusion into a peripheral compartment (V_t) [(31); Yiew, Bateman, Hahn, Bersenas, Muir; (179, 198–201)]. The distribution half-time for most crystalloids is relatively short (<8–10 min) implying that distribution is complete within ∼30–50 min (4–5 half-lives), a range that closely coincides with the measured half-lives reported for acetated (56 min) and lactated (50 min) Ringer's solutions in humans (155). A low Cl_d from V_c increases the infused fluid's potency (i.e., the volume required to expand the plasma volume by 20% in 30 min) but also increases hemodilution. The Cl_d for colloidal solutions [i.e., hydroxyethyl starches (HES)] is much lower than crystalloids, suggesting delayed departure from V_c and prolongation of their volume expanding effects.

Rapid fluid administration rates (>40–60 ml/kg/hr) and large fluid volumes (>60–80 ml/kg) produce hemodilution, interstitial fluid accumulation (i.e., edema), and serious rebleeding in animals with uncontrolled hemorrhage (15, 78, 83, 202, 203). Most anesthetic drugs, particularly inhalant anesthetics (e.g., propofol, isoflurane), depress cardiorespiratory function, blunt homeostatic reflexes, promote vasoplegia, [Valverde; (204–206)] decrease tolerance to acute anemia [i.e., increase the critical Hb concentration: (Hb_{crit})] (207, 208), promote interstitial fluid accumulation (209) and perioperative fluid retention (209–212), decrease urine output (212, 213), and depress the response to fluid administration (204, 214). In addition, vasoactive drugs are known to alter fluid volume kinetics (215–219). Stimulation of alpha1- adrenergic receptors (e.g., norepinephrine; phenylephrine) increases V_d, Cl_d, the accumulation of fluid in V_t, and Cl_r while stimulation of beta-1 adrenergic receptors (e.g., isoproterenol) increase V_c and decrease V_d, Cl_d, and Cl_r (69, 216, 217, 220). Notably, fluid accumulation in V_t is more significantly influenced by the rate of infusion (i.e., ml/kg/min) than by the infused fluid volume; higher infusion rates produce greater degrees of interstitial fluid accumulation, hemodilution, coagulation abnormalities, and organ dysfunction (79, 199, 203, 221, 222).

NEW HORIZONS

New fluids and goal directed fluid therapies (GDFT) continue to be developed for the treatment of specific naturally occurring diseases with the goals of improving tissue oxygenation and perfusion [(9); Edwards and Hoareau; (197, 223–228)], and reducing adverse events and mortality (229, 230). Damage control resuscitation (DCR) strategies limit the amount of crystalloids administered and employ balanced blood product resuscitation ratios [PRBC's-plasma-platelets ratio of 1:1:1; Hall and Drobatz; Boysen and Gommeren; (230–235)]. Isotonic and hypertonic crystalloid solutions continue to be investigated in order to rapidly restore hemodynamics, reduce the amount of fluid administered in order minimize hemodilution, and tissue edema, and lessen the development of disseminated intravascular coagulation (58–62, 236, 237). Novel therapies that mimic natural hemostatic mechanisms (68) or reduce vascular leakage (238–240) are being developed and solutions that increase tissue oxygenation (e.g., hemoglobin) and restore microcirculatory blood flow continue to evolve (241–243). Future fluids should protect or repair the endothelium (224, 228, 238, 244, 245). Methods for determining their

success will be dependent upon the development of validated dynamic non or minimally invasive hemodynamic monitoring methodologies [(42); Cooper and Silverstein; Boysen and Gommeren; (20, 38–41, 235, 246–254)] in addition assessment of thromboelastographic variables (249), implementation of deep-learning algorithms (254) and development of bio-responsive drug delivery systems [Gholami et al.; (255–260)]. It is hoped that the information contained within this compendium will inspire readers to employ fluid therapy practices that improve patient outcome.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Terms, Definitions, Nomenclature, and Routes of Fluid Administration

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Fluid therapy is administered to veterinary patients in order to improve hemodynamics, replace deficits, and maintain hydration. The gradual expansion of medical knowledge and research in this field has led to a proliferation of terms related to fluid products, fluid delivery and body fluid distribution. Consistency in the use of terminology enables precise and effective communication in clinical and research settings. This article provides an alphabetical glossary of important terms and common definitions in the human and veterinary literature. It also summarizes the common routes of fluid administration in small and large animal species.

Keywords: intraosseous, subcutaneous, intravenous, terminology, rehydration, fluid therapy, glossary, fluid administration methods

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INTRODUCTION

Fluid therapy is an important component in the treatment of many hospitalized veterinary patients. The breadth of literature on fluid therapy-related concepts and management strategies is continually expanding and clarity in the use of the terminology is essential for effective communication and patient care. Using incorrect terms can lead to misunderstanding, misinterpretations, and inappropriate therapeutic decisions. The first aim of this article is to provide a glossary of key terms with reference to definitions found in the veterinary and human medical literature. Commonly used abbreviations, synonyms, and related words are listed after the associated term, where applicable. An expanded definition is provided for any term for which there is no widely accepted definition. The second aim of this article is to describe the different routes of fluid administration in veterinary species.

METHODS

For the glossary, a list of fluid therapy related terms was compiled based on common terms encountered in the fluid therapy literature pertaining to intravenous fluid classifications, intravenous fluid administration strategies, body fluid volume and hydration, body fluid compartments, body fluid composition, and acid-base balance. A systematic PubMed/MEDLINE search and literature review of the veterinary and human medical literature was performed between January to October 2020 to search for individual terms in the title, key words or abstract. The full glossary term was used as the search term by itself, individually as well as with the addition of the following words: "definition," "veterinary," and if needed, included terms denoting to specific veterinary species such as "dog," "cat," or "horse.". For example, the search strategy for "Acute Normovolemic Hemodilution" used the following search terms: "acute normovolemic hemodilution," "acute normovolemic hemodilution definition," "acute normovolemic hemodilution veterinary," "acute normovolemic hemodilution dog" and "acute

normovolemic hemodilution cat." Publications were considered if they were available in English and were published or in press. A minimum of 3 articles were reviewed for each search term, up to a maximum of 6 articles. Priority was given to articles from journals with a high impact factor, veterinary journals, and consensus-type articles, as well as the most recently published definitions. Case reports, comments, editorials and letters to the editor were excluded because they rarely contained definitions. The full text of all identified articles were screened for definitions to one or more glossary terms and multiple articles were evaluated in order to determine the degree of agreement. If the literature search revealed inconsistencies in the definition for any particular term, the literature search was expanded, and the most commonly encountered definition was provided with the addition of a notation mentioning the lack of widespread consensus. Where multiple similar terms could be used describe the same concept, the most frequently encountered term was listed in the glossary and synonyms were provided at the end of the applicable definition.

RESULTS

Glossary of Terms

Absolute Hypovolemia

A reduction in total circulating blood volume. Absolute hypovolemia can be caused by dehydration (i.e., water and electrolyte loss) or the loss of blood from the body or into a body cavity (e.g., abdomen) (1, 2).

Acid

A substance that is capable of increasing the concentration of hydrogen ions (H^+) when dissolved in water (aqueous solution) (3).

Acidemia

A blood pH that is below the normal physiologic range for the species in question (4).

Acidosis

A process in which there is a net accumulation of acid in the body (3).

Acute Normovolemic Hemodilution

A blood conservation strategy where a specific volume of whole blood is removed from the patient and stored, and replaced by sufficient volumes of crystalloid or colloid solutions to restore intravascular volume prior to surgery. The rationale of this technique is to reduce the loss of red blood cells from surgical bleeding through hemodilution, thereby lowering the need for allogenic blood transfusions. The reserved blood is subsequently returned to the patient during or after surgery (5). Synonym: *isovolemic hemodilution*.

Albumin

Circulating blood protein weighing 69 kDa that is synthesized by the liver and is the major determinant of plasma oncotic pressure (6).

Alkalemia

A blood pH that is above the normal physiologic range for the species in question (4).

Alkalosis

A process in which there is a net accumulation of alkali in the body (7).

Anion

A negatively charged atom or molecule, such as chloride (Cl^-) and bicarbonate ($HCO3^-$) (8).

Anion Gap (AG)

The calculated difference between the principle cations and anions in plasma. Anion gap is calculated by the following formula: $AG = (Na^+ + K^+) - (Cl^- + HCO3^-)$. Anion gap is useful to help narrow down the potential causes of metabolic acidosis (4, 8).

Autotransfusion

A blood conservation strategy used during hemorrhage or surgery where shed blood is collected, typically mixed with anticoagulant, filtered and reinfused into the patient (9). In human medicine, where it is typical to wash red blood cells prior to readministration, this process is also referred to as *blood salvage* or *cell salvage*.

Balanced Component Resuscitation

A fluid resuscitation strategy in severe trauma management where blood products are transfused in proportions similar to blood (1:1:1 ratio for packed red blood cells, plasma and platelets) (10, 11). Synonym: *balanced resuscitation*.

Balanced Crystalloid Solution

A fluid that contains an electrolyte composition (particularly sodium, potassium, and chloride) that is similar to that found in plasma. A balanced solution should maintain or normalize acid-base balance and be isosmotic and isotonic (i.e., not induce inappropriate fluid shifts) with normal plasma (4, 12, 13). Synonyms: *balanced isotonic electrolyte solution, polyionic crystalloid solution,* or *balanced salt solution.*

Base

A substance that is capable of accepting a hydrogen ion (H^+) when dissolved in water (3).

Base Deficit

The amount of a strong base that must be added *in vitro* to 1 L of oxygenated blood to return the pH to 7.40, at a partial pressure of carbon dioxide of 40 mmHg, and temperature of 37°C, in the presence of metabolic acidosis (14). Represents a deficiency of base, or the negative form of base excess, where a BD of +1 mmol/L is equivalent to a BE of −1 mmol/L.

Base Excess

The amount of a strong acid in mmol/L that must be added *in vitro* to 1 L of oxygenated blood to return the pH to 7.40, at a partial pressure of carbon dioxide of 40 mmHg, and temperature

of 37°C, in the presence of metabolic alkalosis (14). See also *standard base excess*.

Blood Volume
The total volume of blood contained within the circulatory system (15). Synonym: *vascular volume, intravascular volume*.

Buffered Crystalloid Solution
An intravenous fluid containing an acid-base buffer in order to help maintain or restore physiologic pH. This consists of an aqueous solution containing a mixture of electrolytes and a weak acid and its conjugate base. The most common buffers are bicarbonate or organic anions (e.g., lactate, acetate, gluconate) (4).

Cation
A positively charged atom (e.g., Na^+, K^+, Ca^{2+}) or molecule (NH_4^+) (7, 8).

Cell Salvage
See *autotransfusion*.

Central Venous Pressure (CVP)
Measurement of venous blood pressure within a large central vein, or more specifically, the cranial or caudal vena cava (16). A controversial method of assessing right ventricular preload, CVP is not correlated with total blood volume and it is not a good general predictor of fluid responsiveness (17, 18).

Colligative Properties
Alterations in the properties of a solvent due to the addition of solutes. Colligative properties depend on the concentration of molecules in solution, rather than the type of chemical species present (19, 20). Examples include vapor pressure, boiling point, freezing point, and osmotic pressure.

Colloid
Large molecular weight molecules (>30 kDa) that are preferentially retained in the intravascular space following intravenous administration. Types of natural colloids include plasma and albumin. Synthetic colloids include hydroxyethyl starches, dextrans, and gelatins (7, 21).

Colloid Osmotic Pressure
The osmotic force generated by large molecules (colloids) in solution when separated by a semipermeable membrane from a region with a different colloid concentration (22). The colloid osmotic pressure provided by plasma proteins is also referred to as *oncotic pressure*.

Colloid Solution
An intravenous fluid containing macromolecules dispersed in a crystalloid solution. It is administered to support intravascular volume or raise plasma colloid osmotic pressure (23–25). Natural colloid solutions include blood products and albumin. Synthetic (or artificial) colloid solutions include hydroxyethyl starches, dextrans and gelatins. Colloid fluid therapy is also referred to as *biophysical therapy* (26).

Constant Rate Infusion (CRI)
Continuous intravenous administration of a medication in order to maintain a steady delivery or plasma concentration (27).

Critical Hematocrit
The minimum hematocrit that supports adequate tissue oxygenation and below which organ ischemia will develop (28, 29).

Crystalloid
A solution that contains electrolytes and other small water soluble molecules, and/or dextrose. Crystalloids are categorized by their tonicity relative to plasma: isotonic, hypotonic, and hypertonic (23–25).

Cumulative Fluid Balance
The difference between all fluid inputs and outputs over a defined period of time (30, 31). Cumulative fluid balance over a 24-h period is also referred to as *daily fluid balance*.

Daily Fluid Balance
The difference between all fluids inputs and outputs during a 24-h period, generally excluding insensible losses (30, 31). Daily fluid balance can be negative, neutral or positive.

Damage Control Resuscitation
A resuscitation strategy used to treat severely traumatized patients in order to reduce the development of the "lethal triad" of hypothermia, coagulopathy and acidosis (32, 33). The key principles are the early use of blood products, avoidance of excessive crystalloid infusions which can cause dilutional coagulopathy, and permissive hypotension (32, 33).

Deescalation
Reduction of fluid administration due to clinical improvement of the patient (31).

Dehydration
The loss of body water, with or without salt, at a rate greater than the body can replace it (34–36).

Deresuscitation
Correcting fluid overload by using dialysis or diuretics to remove excess fluid (37, 38).

Early Goal-Directed Therapy
A protocol-driven treatment algorithm that aims to guide fluid, vasopressor, and other resuscitation therapy toward specific hemodynamic end-points, with the goal of optimizing oxygen delivery (24, 39). Originally developed for the treatment of patients with sepsis (39), the concept has since been adopted for the treatment of critically ill patients with other conditions as well as in perioperative settings (40). "Early" refers to its use during the initial stabilization period, otherwise it is described as *goal-directed hemodynamic therapy*.

Edema
Clinical manifestation of fluid accumulation within the interstitial tissue space (interstitial edema) or within cells (cellular edema) (41, 42).

Effective Osmole
An electrolyte (ion) that exerts an osmotic force (i.e., pull) across a semi-permeable membrane. Effective osmoles determine a solution's tonicity. Sodium ion is the predominant effective osmole in the body (43).

Electrolyte
Dissolved ions in solution that carry a positive or negative electric charge, such as sodium, potassium, chloride, and calcium (35).

Endothelial Glycocalyx (EG)
A negatively charged, mesh-like layer on the luminal surface of vascular endothelial cells, composed of membrane-bound glycoproteins and proteoglycans, which have an important role in regulating vascular permeability, endothelial anticoagulation and modulating interactions between the endothelium and the vascular environment (9, 44–46). EG damage and breakdown are particularly susceptible to fluid overload, catecholamine-induced damage and shock (46).

Euvolemia
Normal circulating blood volume (35, 47).

Fluid Administration
Delivery of fluids to a patient through an enteral or parenteral route (48). The rate of fluid administration should be described in ml/kg/min or ml/kg/h. Fluid rates described in ml/h or ml/min are meaningless unless they are referenced to body weight or body surface area. The duration of infusion should be stated in order to determine the total volume of fluid administered.

Fluid Balance
The net difference between bodily fluid gains or inputs (including enteral, subcutaneous and intravenous fluids, injectable medications, and blood products) and fluid losses or outputs (including urinary, gastrointestinal, blood losses) over a specified time period (49, 50). Insensible losses are usually omitted (30). Fluid gains exceeding fluid losses represents a positive fluid balance, whereas fluid losses exceeding gains lead to a negative fluid balance. Fluid balance can be expressed as a volume or as a percentage of body weight. Related terms: *daily fluid balance, cumulative fluid balance.*

Fluid Bolus
Rapid intravenous administration of a small or large volume of fluid for the purpose of restoring tissue perfusion, such as during the treatment of hypovolemic shock (31, 51–53).

Fluid Challenge
Rapid intravenous administration of a modest volume of fluid, usually a crystalloid, in order to assess the likelihood of volume-responsiveness in a patient with hemodynamic instability, while minimizing the risk of fluid overload (31, 54). A fluid challenge is typically followed by a fluid bolus in patients that exhibit a positive response to the fluid challenge.

Fluid Compartments
Describes the distribution pattern of total body fluid within several well-defined spaces separated from each other by cell membranes (55). Together, the intravascular and interstitial fluid compartments comprise the extra-cellular fluid space and contain approximately one-third of the total body water, while intracellular fluid compartment contains approximately two-thirds of the total body water (55).

Fluid Creep
This term has two different situation-dependent meanings. Fluid creep describes the administration of IV fluid to burn patients in excess of fluid requirements calculated by the Parkland Formula (56, 57). This is done in an effort to optimize hemodynamic status but may increase the risk of edema formation. Fluid creep also refers to the unintentional and unmeasured fluid volumes administered in the process of delivering medication and nutrition through enteral and parenteral routes during maintenance fluid therapy or undocumented oral fluid intake (58).

Fluid Infusion
Intravenous fluid administration (31).

Fluid Overload
An increase in total body fluid (typically both water and electrolytes) in excess of physiologic requirements. Some publications define it as a 10% or more increase in total body weight due to fluid administration which represents the threshold for an increased risk of adverse clinical effects such as pulmonary edema, peripheral edema or body cavity effusion (30, 31, 59–61). This non-specific term is loosely used and in some cases may be replaced by more specific concepts, such as *volume overload*, which refers to excess fluid in the intravascular fluid compartment, or *overhydration*, which describes excessive pure water gain in the body.

Fluid Responsiveness
The ability for hemodynamic parameters to improve in response to a fluid challenge or bolus (51, 62). There is some variability in the specific parameters and magnitude of change that are considered consistent with a positive response. However, many definitions consolidate around an increase in cardiac output (51, 62) or stroke volume (52, 54) by at least 10–15% from baseline following administration of a fluid bolus that is delivered over <15 (51, 52) or 30 min (53). Others consider a patient to be fluid responsive if there is a significant change in one or more of the following: increase in mean arterial pressure of more than 10 mm Hg, decrease in heart rate of more than 10 BPM, increase in central venous pressure (>2 cm H_2O) or an increase urine output (53, 63).

Fluid Resuscitation
The administration of intravenous fluids to reverse life-threatening tissue hypoperfusion (31, 62). Synonym: *volume resuscitation*.

Fluid Retention
An increase in net fluid balance resulting accumulation of excess fluids in body tissues and weight gain (64–66) and in some cases, peripheral edema (66). This is due to physiological or pathological processes promoting renal reabsorption and fluid conservation, such as during dehydration, pregnancy, anesthesia, acute kidney injury (AKI) and congestive heart failure (64).

Fluid Therapy
The unnatural process of administering fluids as a treatment or preventative measure to maintain or restore normal body fluid balance.

Fluid Titration
Adjustment of intravenous fluid administration choice, rate, volume and timing in order to improve hemodynamics and optimize tissue perfusion (31).

Fluid Underload
Decrease in total body fluid, resulting in fluid deficit of the extracellular and/or intracellular fluid (67). The opposite of *fluid overload*.

Goal-Directed Therapy (GDT)
The use of advanced non-invasive and invasive monitoring techniques in conjunction with intravenous fluids, vasopressors or inotropes with the goal of maintaining or establishing hemodynamic stability, adequate tissue perfusion and oxygen delivery to tissues (68, 69).

See *early goal-directed therapy*.

Hemodynamic Coherence
Coherence between macrocirculatory and microcirculatory hemodynamics such that regional and microcirculatory perfusion and tissue oxygen delivery permits normal cellular function in support of organ function (70, 71).

Hemoglobin-Based Oxygen Carrier (HBOC)
A cell-free hemoglobin solution used in veterinary medicine in the 1990's and 2000's as a blood transfusion substitute to improve oxygen carrying capacity (72–74). HBOC's solutions are not commercially available in the US. Synonym: *oxygen therapeutics*.

Hyperchloremic Metabolic Acidosis
Hyperchloremia accompanied by hypobicarbonatemia and metabolic acidosis. Two different mechanistic explanations are bicarbonate loss or dilution (Henderson-Hasselbalch approach) (13) or a decrease in SID caused by an increase in chloride (i.e., 0.9% Na^+Cl^-) (4, 13, 75). Synonym: *normal anion gap acidosis.*

Hyperoncotic Colloid
A colloid solution with an oncotic pressure above that of plasma (e.g., 10% hydroxyethyl starch, 20% human albumin) (76).

Hyperperfusion
Increased (supraphysiologic) blood flow to the tissues (35).

Hypertonic Crystalloid
A crystalloid solution with a higher effective osmolality than plasma (e.g., 7.2% sodium chloride: 2464 mOsm/L) (23).

Hypertonic Saline (HS)
A sterile hypertonic intravenous crystalloid composed of water, sodium and chloride. Available in multiple concentrations including 3%, 5% and 7.2% (77, 78).

Hypertonic-Hyperoncotic Solution
A resuscitation fluid containing a hypertonic crystalloid (>310 mosmol) and a hyperoncotic (>5%) colloid that is used as an alternative small volume fluid resuscitation strategy to rapidly increase intravascular fluid volume in the treatment of hypovolemia [e.g., 7.5% saline and 6% Dextran-70 (HSD)] (79, 80). Synonym: *turbostarch.*

Hypervolemia
Excessive circulating blood volume (52, 61). See also *fluid overload.*

Hypooncotic Colloid
A colloid solution with an oncotic pressure below that of plasma (e.g., 4% human albumin) (76).

Hypoperfusion
Insufficient blood flow to the tissues, resulting in decreased oxygen delivery. End-organ hypoperfusion can manifest as cool extremities, reduced pulse quality, oliguria and tachycardia (81, 82).

Hypotensive Resuscitation
See *permissive hypotension.*

Hypotonic Crystalloid
A crystalloid solution with a lower effective osmolality than plasma (e.g. 0.45% sodium chloride: 154 mOsm/L) (23). A solution of 5% dextrose in water is also classified as a hypotonic fluid despite having an osmolality (278 mOsm/L) that is similar to plasma, since the dextrose is rapidly taken up into cells and metabolized following infusion, leaving water behind (48).

Hypovolemia
Insufficient intravascular fluid volume, which may be absolute such as from dehydration and hemorrhage, or relative such as with vasodilatory shock (61, 83).

Ineffective Osmoles
Small dissolved particles in solution that contribute to total osmolality but do not exert an osmotic pressure because they freely cross and equilibrate across cell membranes (e.g., urea, dextrose) (84).

Insensible Water Loss
Body fluid losses that cannot be easily measured, such as evaporative losses from the skin and respiratory tract, and the water content of stool (85, 86).

Interstitial Fluid
The total volume of extracellular fluid contained within the interstitial tissues surrounding cells (12–15% of total body weight) (55).

Intracellular Fluid
The total volume of fluid contained within cells (40% of total body weight) (55).

Intravascular Fluid
The total volume of extracellular fluid contained within arteries, veins and capillaries in the circulatory system (6–8% of total body weight) (55).

Intravascular Volume Depletion
Reduction in intravascular fluid volume, which is a type of extracellular fluid volume depletion (87). Related term: *volume depletion*.

Isooncotic Colloid
A colloid solution with an oncotic pressure similar to that of plasma (e.g., 6% hydroxyethyl starch, 5% human albumin) (88).

Isotonic Crystalloid
A crystalloid solution with an osmolality similar to plasma. The two types of isotonic crystalloids are isotonic saline (0.9% sodium chloride) and balanced solutions (e.g., lactated Ringer's, Normosol®-R) (13).

Isovolemic Hemodilution
See *acute normovolemic hemodilution.*

Lactic Acidosis
Hyperlactatemia with concurrent metabolic acidosis (89–93). Lactate is produced by skeletal muscle and other tissues in large amounts during anaerobic conditions and is commonly used as a marker of the adequacy of tissue perfusion (Type A lactic acidosis). Increased production of L-lactic acid in the absence of hypoxia or increased demand for ATP is termed Type B lactic acidosis. Notably, rapid intravenous administration of lactated Ringer's solution increases plasma lactate concentration within 10 min but baseline values are reestablished within 60 min after cessation of administration (93).

Lean Body Mass
Total body weight minus the weight of fat. Calculated as 80% of ideal body weight when 20% of total body weight is fat (94).

Liberal vs. Restrictive Fluid Therapy
Term applied to randomized trials investigating the effect on morbidity and mortality of a conservative (restrictive) fluid strategy, compared to a standard (liberal) fluid regimen. Many standard fluid regimens are more likely to result in a positive fluid balance (95–97).

Macrocirculation
Large and medium-sized arteries and veins that serve as conduit vessels, transporting blood to and from organs and tissues (98).

Maintenance Fluid
A type of crystalloid solution that is designed to maintain hydration by meeting daily water and electrolyte requirements (7, 23, 86). Both hypotonic and isotonic fluids can fulfill these requirements (86).

Maintenance Fluid Therapy
A fluid therapy plan designed to provide water and electrolytes in quantities that meet normal daily fluid needs and replace urinary, gastrointestinal, and evaporative losses (86).

Massive Hemorrhage
Loss of > 40–50% of total blood volume over 3 h or less, or > 100% of total blood volume over 24 h (99).

Massive Transfusion
Replacement of > 40-50% of total blood volume over 3 h (11, 99), or > 100% of total blood volume over 24 h (100, 101).

Microcirculation
Blood vessels <200–300 micrometers in diameter, consisting of small arteries, arterioles, capillaries, and venules (98, 102–104).

Normal Anion Gap Metabolic Acidosis
See *Hyperchloremic metabolic acidosis.*

Normal Saline (NS)
See i*sotonic saline.*

Normovolemia
See *euvolemia.*

Oncotic Pressure
See *colloid osmotic pressure.*

Osmolality
A measure of the concentration of osmotically active particles per unit volume of solution, measured in milliosmoles per liter of solution (mOsm/L) (7, 22, 105). In clinical practice, osmolarity, and osmolality are similar enough to be used interchangeably (106).

Osmolarity
A measure of the concentration of osmotically active particles per unit mass of solution, measured in milliosmoles per kilogram of solution (mOsm/kg) (7, 22, 105). In clinical practice, osmolarity, and osmolality are similar enough to be used interchangeably (106).

Osmosis
The process by which molecules of a solvent tend to pass through a semipermeable membrane from a less concentrated solution into a more concentrated solution, thus equalizing the concentrations on both sides of the membrane (20).

Parenteral
Administration of food or medication through a non-enteral (e.g., non-oral) route, such as intravenous, subcutaneous, intramuscular and intradermal (107).

Parkland Formula
A fluid resuscitation protocol for burn patients which calls for lactated Ringer's solution dosed at 4 ml/kg/%TBSA, where %TBSA refers to the percentage of the total body surface area burned (108, 109). Half of the volume is delivered over the first 8 h and the remainder over the next 16 h .

Perfusion
The passage of fluid through the circulatory system to organs and tissues (103, 110).

Permissive Hypotension
A fluid therapy technique that aims to provide enough resuscitation fluid to ensure adequate end-organ perfusion while maintaining mild hypotension (systolic pressures <90 mmHg) until definitive hemorrhage control can be achieved (32, 33, 111). Synonym: *hypotensive resuscitation*.

Plasma
The liquid portion of blood that remains after the cells are removed. Plasma is retrieved by centrifugation of an anticoagulated blood sample, and so unlike serum, it contains fibrinogen and clotting factors (112).

Pleth Variability Index (PVI)
An automatic measure of the dynamic change in perfusion index (PI), as determined by a pulse oximeter, occuring during a complete respiratory cycle. The pulse oximeter derived pulsatile signal is indexed against the non-pulsatile infrared signal and expressed as a percentage [PI = (AC/DC) × 100] reflecting the amplitude of the pulse oximeter waveform. The pulse variability index is calculated as PVI = [(PImax – PImin)/PImax] × 100 (113).

Polyionic Crystalloid Solution
See *balanced crystalloid solution.*

Proteid
A complex biomolecule predominantly made of polypeptides that is found in all living matter (114).

Pulse Pressure (PP)
The difference between arterial systolic and diastolic blood pressure measured in millimeters of mercury (mm Hg) (115).

Pulse Pressure Variation (PPV)
The difference between the maximum (PPmax) and minimum (PPmin) arterial pulse pressures during one respiratory cycle, divided by their sum divided by 2 ([PPmax + PPmin]/2) and expressed as a percentage (116). Pulse pressure variation is used as a predictor of fluid responsiveness in mechanically ventilated patients.

Pulse Wave Transit Time (PWTT)
Time needed for a pulse wave to travel between two arterial sites (117). Due to its inverse relationship to stroke volume, it can be used to assess changes in cardiac output and to evaluate fluid responsiveness in dogs after a fluid challenge (117). It also serves as a marker of arterial stiffness in humans with coronary artery disease (118). PWTT can be calculated as the time from the peak of the R-wave on an electrocardiogram to the rise point of the pulse oximeter wave (the point where it attains 30% of its maximal amplitude) (119).

Rebound Hypovolemia
Hypovolemia produced by diuresis induced by rapid bolus fluid administration to conscious animals (120).

Relative Hypovolemia
A reduction in the effective circulating blood volume due to venodilation and increased venous capacitance (2). Relative hypovolemia can be caused by drug toxicity (e.g., sensitivity to anesthetic drugs or anesthetic overdose), impairment or loss of compensatory mechanisms, coexisting or induced metabolic or respiratory acidosis, traumatic or surgically induced inflammation, sepsis, cardiogenic shock, and hypothermia.

Replacement Fluid
A type of crystalloid solution that is isotonic, has a composition similar to extracellular fluid, and is administered to replace water and electrolyte losses (e.g., Normosol-R, lactated Ringer's, Plasma-Lyte 148) (7, 23).

Rescue, Optimization, Stabilization, and Evacuation (ROSE)
A conceptual framework that describes four different stages of fluid resuscitation, beginning with initial rapid fluid administration to treat life-threatening shock (Rescue), continued fluid therapy until adequate perfusion is restored (Optimization), followed by ongoing maintenance fluids (Stabilization), and gradual discontinuation of fluid support (i.e., Evacuation or De-escalation) (31, 109, 121).

Resuscitation
See *fluid resuscitation*.

Revised Starling Equation
An updated version of the traditional Starling equation that incorporates current understanding of the role of the endothelial glycocalyx in transvascular fluid filtration (44, 122, 123). Related term: *Starling Principle*.

Sensible Water Loss
Measurable body fluid losses, such as urine, vomit, and diarrhea (85, 86).

Shock
A life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells, resulting in cellular dysfunction (124). Shock is most commonly organized into four major classifications that have different pathophysiological mechanisms: *hypovolemic shock* refers to reduced effective circulating volume, from internal

or external intravascular fluid loss (125); *obstructive shock* results from physical impairment to blood flow, such as from thromboembolic disease; *distributive shock* is caused by maldistribution of blood flow due to loss of vasomotor tone, such as during sepsis or anaphylaxis (124); c*ardiogenic shock* describes cardiac pump dysfunction resulting in decreased forward flow (124, 126).

Shock Index (SI)

Calculated as the ratio of the heart rate (HR) divided by systolic blood pressure (SBP) (127). SI >1.0 is a predictor of increased risk of mortality and other markers of morbidity (128).

Skin Turgor

The relative elasticity of the skin, used as an estimate of hydration status (129, 130). Skin turgor is evaluated by tenting the skin with the fingers and timing its return to its normal form. Dehydration and increasing age are associated with decreased skin turgor (34).

Standard Base Excess (SBE)

The amount of strong acid (millimoles per liter) that needs to be added *in vitro* to 1 L of fully oxygenated whole blood to return the sample to standard conditions (pH of 7.40, PCO_2 of 40 mm Hg, and temperature of 37°C), at a hemoglobin concentration of ∼50 g/L (14, 131). Unlike base excess, standard base excess has been adjusted to reflect the extracellular fluid buffering capacity of hemoglobin *in vivo*. It is used clinically to determine the degree of metabolic acidosis.

Synonym: *base excess of the extracellular fluid (BE_{Ecf})*. Related term: *base excess*.

Starling Principle

Fluid flux across the capillary wall is determined by a balance of hydrostatic and oncotic pressures such that fluid leaves the capillary at the arterial end of the capillary and is absorbed at the venous end of capillary (123).

Stressed Vascular Volume (Vs)

The volume of blood within a vein that produces a transmural pressure above zero (52, 132). Compare to *unstressed vascular volume*.

Stroke Volume Variation (SVV)

The difference between maximum and minimum stroke volume during one respiratory cycle, divided by their mean, and averaged over several breaths (133). Stroke volume variation is used as an indicator of fluid responsiveness in mechanically ventilated patients.

Strong Ion

A cation and anion that are considered to be fully dissociated at physiologic pH (13, 131, 134, 135). The major strong cations in plasma are sodium, calcium and magnesium, while the major strong anions are chloride, sulfate, and lactate.

Strong Ion Difference (SID)

The difference between the concentrations of strong cations and strong anions in plasma (134–136).

Strong Ion Gap (SIG)

SIG quantifies [unmeasured anions] – [unmeasured cations] of both strong and weak ions. It is reflects the difference between the activity of all common cations (Na^+, K^+, Mg^{2+}, Ca^{2+}) with the common anions (Cl^-, lactate, urate) and other measured non-volatile weak acids (A^-). SIG is calculated as SIDa – SIDe, or more specifically, as $[Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-$ corrected] – [lactate] - $[A^-]$ – $[HCO_3^-]$, in milliequivalents per liter; where SIDa is the apparent strong ion difference and SIDe is the effective strong ion difference (137). An increased SIG is a predictor of mortality (8).

Third Spacing

The pathological shift of fluid into extracellular sites in the body that are anatomically separated from other body fluid compartments and where the fluid is considered to have no physiological function (138–140). In human patients, the fluid movement is theorized to occur following trauma or major surgery into ill-defined spaces following intravenous fluid administration. However, these "spaces" have since been identified to include interstitial fluids. Third space fluids are eventually reabsorbed into the central fluid compartment and are therefore considered to be a myth (139, 140). In veterinary medicine, the term is also used to refer to the loss of fluids into body cavities, such as the pleural space, peritoneal space and gastrointestinal lumen (141).

Titration

See *fluid titration*.

Tonicity

A measurement of the effective osmolality of a solution, which corresponds to its ability to cause water to diffuse across a semi-permeable membrane, such as the cell membrane (20, 142–144). A cell will swell when placed in a hypotonic solution, shrink when placed in a hypertonic solution, and have an unchanged volume in an isotonic solution.

Total Body Water

The total water content in the body, which represents the sum of the intracellular and extracellular fluid volumes (43, 52). Total body water is ∼60% of ideal body weight in adult dogs (55), cats (55), and horses (145).

Unstressed Vascular Volume (Vu)

The volume of blood in a vein that produces a transmural pressure equal to zero (52, 132). The sum of the stressed (∼30% of total volume) and unstressed (∼70% of total volume) volumes is the total blood volume within the venous system (132). Compare to *stressed vascular volume*.

Vascular Hyporesponsiveness

A decreased vascular response to fluid therapy or the pressor effects of exogenous vasopressors (146). Vascular reactivity to the administration of catecholamines or other vasopressors (e.g., vasopressin) is used to predict mortality (146, 147).

Vascular Volume

See *blood volume*.

Vasoplegia
Severely low systemic vascular resistance in conjunction with profound hypotension and a normal or increased cardiac output (148). Occasionally referred to as vasoplegic shock and used synonymously with distributive shock, the vasoplegic syndrome may occur in septic shock, after surgery, burns, severe pancreatitis or extensive trauma (148).

Volume Depletion
The loss of water and electrolytes from the extracellular fluid compartment (34). Volume depletion can be classified by the location of the lost fluid, such as intracellular dehydration or extracellular fluid loss. It can also be characterized by the salt and water content of the fluid loss. *Hypotonic fluid loss*: A predominantly pure water deficit which is caused by water loss exceeding solute loss in the extracellular fluid, or by insufficient water intake relative to water output, leading to hypernatremic volume depletion. *Hypertonic fluid loss*: A deficit of water and solutes from the extracellular fluid, where the solute loss exceeds water loss, resulting in the development of hypoosmolality of the extracellular fluid and hyponatremic volume depletion. *Isotonic fluid loss*: A proportionate deficit of water and solutes from the extracellular fluid, therefore the osmolality of the extracellular fluid does not increase.

Volume Kinetics
The study of how water is distributed and eliminated following an infusion of intravenous fluids (149, 150).

Volume Overload
See *fluid overload.*

Zero Balance Fluid Therapy
A restrictive regimen aiming to avoid postoperative fluid retention (as indicated by weight gain) (151, 152).

Routes of Fluid Administration
Fluids are typically administered to veterinary patients through enteral, subcutaneous and intravenous routes (23, 48, 153), or less commonly, into the medullary cavity (154) or into the coelom in reptiles (155). The ideal method of fluid delivery will vary depending on the species, the underlying disease processes, and the size of the fluid deficit. Animals that require rapid correction of life threatening conditions, such as hypovolemic shock, benefit from the rapid intravascular volume expansion achievable with intravenous fluids. On the other hand, non-intravenous fluid delivery routes, which are characterized by slower rates of absorption (156), may be sufficient in stable patients to meet maintenance fluid needs, treat lesser degrees of dehydration or keep up with abnormal ongoing losses.

Subcutaneous or enteral fluids can be considered in small animal patients with mild to moderate fluid deficits. Compared to intravenous fluid administration, there is a lower limit to the amount of fluid that can be delivered by these routes. In the presence of severe dehydration and hypovolemia, avoid fluid replacement by the subcutaneous route due to the potential for decreased absorption resulting from peripheral vasoconstriction (7, 48).

Where larger volumes of fluid are necessary but venous access cannot be obtained (a common dilemma in many pediatric, avian, and exotic animals), placement of an intraosseous (IO) catheter may be considered (154, 157). Despite increased resistance to flow compared to intravenous infusion, reasonably high fluid administration rates can still be achieved with intramedullary delivery (158). The gravity-dependent rate of fluid delivery was greater in the femur and humerus compared to the tibia and ilium in one canine cadaveric study (159).

When voluntary oral intake is insufficient or undesirable, fluids can be rapidly and inexpensively administered by nasogastric tube to horses (153, 160) and ruminants (161, 162) to treat mild to moderate dehydration. In some cases, parenteral methods may be preferred in camelids to reduce stress (163). As with companion animal species, intravenous fluids are preferred when severe dehydration is present due to the potential for reduced bowel absorption resulting from hypoperfusion (153).

Alternative fluid administration sites have also been described. A 6-h crystalloid infusion given per rectum was reported to be safe and well-tolerated in horses (156), although the usefulness of this technique in clinical settings remains undetermined. Unlike in reptiles, where intracoelomic fluid delivery is well-described (155), intraperitoneal fluid administration is rarely discussed or performed in other species (48) due the presence of safer alternatives.

DISCUSSION

Despite the frequency with which fluids are administered to veterinary patients, developing an effective fluid management plan may at times be surprisingly complex. A thorough understanding of the physiology of body fluids, fluid administration routes, therapeutic delivery strategies, risks, and complications will help to optimize patient outcomes. National and multinational organizations, such as the International Fluid Academy (IFA), provide opportunities for clinicians and researchers to promote research and education in the practice of fluid therapy. The use of clear and consistent terminology is a key component to fostering effective communication and collaboration within the veterinary and human healthcare fields.

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REVIEW
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A Modern View of the Interstitial Space in Health and Disease

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Increases in the volume of the interstitial space are readily recognized clinically as interstitial edema formation in the loose connective tissue of skin, mucosa, and lung. However, the contents and the hydrostatic pressure of this interstitial fluid can be very difficult to determine even in experimental settings. These difficulties have long obscured what we are beginning to appreciate is a dynamic milieu that is subject to both intrinsic and extrinsic regulation. This review examines current concepts regarding regulation of interstitial volume, pressure, and flow and utilizes that background to address three major topics of interest that impact IV fluid administration. The first of these started with the discovery that excess dietary salt can be stored non-osmotically in the interstitial space with minimal impact on vascular volume and pressures. This led to the hypothesis that, along with the kidney, the interstitial space plays an active role in the long-term regulation of blood pressure. Second, it now appears that hypovolemic shock leads to systemic inflammatory response syndrome principally through the entry of digestive enzymes into the intestinal interstitial space and the subsequent progression of enzymes and inflammatory agents through the mesenteric lymphatic system to the general circulation. Lastly, current evidence strongly supports the non-intuitive view that the primary factor leading to inflammatory edema formation is a decrease in interstitial hydrostatic pressure that dramatically increases microvascular filtration.

Keywords: interstitial pressure, extracellular matrix, lymphatic system, edema, shock, inflammation, sodium balance

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INTRODUCTION

The traditional view that the interstitial space is a relatively static and, frankly, uninteresting region is being reassessed in light of new research showing that the interstitium plays an active role in the regulation of interstitial volume and content and is a key participant in the pathogenesis of inflammation and shock. The passive view holds that changes in interstitial volume and pressure are the result of influences outside of the interstitium, i.e., microvascular pressure, microvascular permeability or plasma colloid osmotic pressure. We now know, however, that the generally predictable relationship between interstitial volume and interstitial pressure can change markedly and that these transitional episodes can occur within minutes. On another front, recent investigations have revealed that the interstitial space plays an active role, in addition to the kidney, in the regulation of salt and water balance in the body including blood pressure. A third avenue of inquiry has confirmed that the intestinal interstitial space and mesenteric lymphatic system provide a critical link between circulatory shock and the subsequent systemic inflammatory response syndrome. This review examines current concepts regarding regulation of interstitial

volume, pressure and flow and, utilizing that background, addresses topics of interest that impact IV fluid administration.

THE INTERSTITIUM

The interstitial space that lies between blood vessels and cells provides the fluid and structural environment surrounding those cells. Under most conditions in most tissues, fluid from the vascular space continually filters from the microvessels into the interstitial space and is not reabsorbed (1). Notable exceptions include the peritubular capillaries in the kidney and microvascular beds within intestinal villi that routinely absorb interstitial fluid (2, 3). Interstitial fluid is removed *via* lymphatic drainage and returned to the venous circulation. In organs located in the pleural, pericardial and peritoneal spaces, some interstitial fluid filters through the organ's serosal surface into the surrounding fluid space and, then, is also taken up into the lymphatic system. In the edematous intestine, interstitial fluid can cross the mucosal barrier into the lumen (4, 5). All of these fluid flows–microvascular filtration, lymph flow, and trans-serosal flow–are significantly influenced by interstitial fluid (hydrostatic) pressure. An increase in interstitial fluid pressure leads to a decrease in microvascular filtration and to increases in lymph flow and trans-serosal flow. Therefore, it is the interplay between all of the factors affecting these flows (i.e., microvascular pressure, lymphatic contractility, serosal permeability, etc.) that determines the steady-state interstitial fluid pressure (6). The interstitial volume is then jointly determined by the interstitial pressure and the interstitial pressure-volume relationship (6).

The structural elements of the interstitial space, collectively called the extracellular matrix, primarily consist of types I and III collagen fibers, elastic fibers, microfibrils, and glycosaminoglycans (GAGs) (7). The GAGs are sulfated (heparin/heparan sulfate, chondroitin/dermatan sulfate and keratan sulfate) and non-sulphated (hyaluronan) (8, 9). The sulfated GAGs are covalently bound to a protein backbone creating a macromolecule called a proteoglycan. These sulfated GAGs carry a net negative charge and are, thus, capable of attracting, and binding cations, such as sodium ions (8, 10).

These interstitial structural elements make distinct mechanical contributions to the relationship between interstitial volume and interstitial fluid pressure. When fibroblasts are cultured *in vitro* in a collagen gel, the fibroblasts attach to the collagen fibers and, by exerting tension on those attachments, reduce gel volume (11). This fibroblast-mediated gel compaction is augmented *in vitro* by platelet-derived growth factor and inhibited by the inflammatory mediators, IL-1α, and PGE_2 (12–14). A comparable effect is seen in the extracellular matrix of loose connective tissue found throughout the body, where fibroblasts attach to multiple collagen fibers *via* integrin connections and compact the matrix (15–18). This action, in concert with the microfibril network, acts to reduce interstitial volume and increase interstitial pressure (19). Conversely, GAGs, particularly hyaluronan, create an imbibition pressure similar to a sponge that acts to expand interstitial volume and decrease interstitial fluid pressure (19, 20). The interstitial fluid pressure-volume relationship and interstitial compliance, i.e., the slope of the interstitial pressure-volume relationship, in part, reflect the interaction between these two counterbalancing mechanical forces (7, 19, 21).

The normal interstitial fluid pressure in tissues such as skin, intestine and lung is subatmospheric on the order of −1 to −4 mmHg; while in other tissues, including liver, kidney, and myocardium, it is normally greater than atmospheric pressure (21–24). In all organs, however, an increase in interstitial volume following increased microvascular pressure and, thus, microvascular filtration is accompanied by an increase in interstitial pressure. This characterizes the normal interstitial pressure-volume relationship and interstitial compliance for each tissue (21, 25).

Protein molecules that filter from the microvasculature into the interstitial space are responsible for the colloid osmotic pressure (COP) exerted by the interstitial fluid. The interstitial protein concentration is determined, in part, by the protein permeability of the microvessels. Due to the high permeability of the hepatic sinusoids, the interstitial protein concentration in the liver is very similar to that of plasma; whereas, the low permeability of the blood-brain barrier ensures a very low protein concentration in the cerebrospinal fluid (26, 27). Interstitial protein concentration is also affected by the microvascular filtration rate. Because of the microvascular barrier's differential permeability to water and protein, an increase in the microvascular filtration rate leads to a fall in the protein concentration of the filtrate, the interstitial fluid and the lymph—a phenomenon called protein washdown (1, 28). Similarly, a decrease in filtration rate results in an increase in interstitial fluid and lymph protein concentrations (28, 29). Once protein has entered the interstitial space, it is removed and returned to the general circulation only by the lymphatic system.

Interstitial compliance in a given tissue is not constant, but rather is a function of interstitial volume. The solid line in **Figure 1** represents the general shape of the interstitial pressure-volume relationship that occurs in tissues like skin and muscle (21). In that figure, we see that, at normal to low volumes, the interstitium has a very low compliance where a small change in volume results in a large change in interstitial fluid pressure (21). At higher volumes, compliance increases allowing interstitial volume to expand with only small increases in pressure. The normal low volume-low compliance state is relevant in understanding the role of interstitial fluid in hemorrhage. In his seminal paper in 1896, Starling commented that it was already well-known that, within a short period following hemorrhage, the blood "contains less hemoglobin and blood corpuscles and relatively more plasma" (31). He concluded that this phenomenon occurs because fluid is absorbed from tissues by the blood vessels. Numerous studies since have confirmed the existence of this hemorrhage-induced shift of interstitial fluid into the vascular space that results from a fall in capillary hydrostatic pressure—a process now called transcapillary refill (32–35). Transcapillary refill is transient however, lasting ∼1 h (32, 35). It is limited by low interstitial compliance because, as fluid is reabsorbed from the interstitial space, interstitial fluid pressure falls. In addition, reabsorption of interstitial fluid into

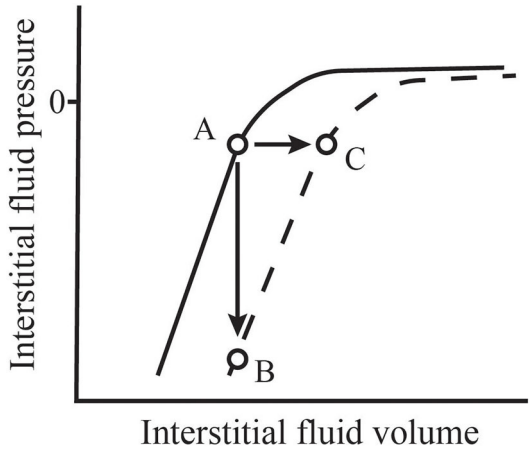

FIGURE 1 | Normal values for interstitial fluid volume and pressure (A) are located along the normal interstitial pressure-volume relationship (solid line). During inflammation, this relationship shifts (dashed line). If microvascular filtration is impeded during this process, thus limiting an increase in volume, interstitial pressure falls precipitously (B). However, if filtration is allowed to continue, the filtration rate may increase 10–20-fold and interstitial volume expands rapidly with little change in pressure (C). Adapted from Aukland and Reed (21) and Stewart (30).

microvessels reverses the protein washdown effect and increases interstitial protein concentration and COP (1). The combined effects of decreased interstitial fluid pressure and increased interstitial COP prevent further fluid reabsorption (1).

The Interstitium in Salt and Water Balance

The conventional view of the regulation of blood volume and pressure has focused on the kidney's ability to regulate total body sodium content (36). More recent information has required an adjustment to that view. While the importance of the kidney in long-term pressure regulation remains unquestioned, it is now known that the interstitial space, particularly of the skin, can actively store sodium in non-osmotic form and, thus, plays an important role in total body sodium and water balance and long-term regulation of blood pressure (37). In 2000, it was reported in a study of human subjects that a high salt diet induced an increase in plasma volume and total body sodium, but no increase in extracellular fluid volume or body weight and no increase in arterial blood pressure (38). Subsequently, a long-term study of humans in simulated space flight that allowed tight control of sodium intake demonstrated no relationship between total body sodium ion and blood pressure (39).

In rats fed a high salt diet, Na^+ storage in skin is increased without a concomitant increase in skin water storage indicating that the sodium is stored non-osmotically (10, 40). In addition, the increased skin sodium content correlated with an increase in the total skin GAG content suggesting that the dermal sodium is stored bound to the negatively charged GAGs within the interstitial space and that the skin GAG content increases adaptively in response to the high sodium load (10). Similarly, a recent study of human subjects demonstrated a positive correlation between the GAG content of skin, artery, and muscle tissue and tissue total sodium levels (41). It was subsequently demonstrated in rats that a high salt diet induced a change in the GAGs in skin toward greater sulfation and higher charge density (42). This change was characterized by an increase in the sulfated GAG-to-hyaluronan ratio. Comparable changes were observed in human heart failure patients that showed increased density of total GAGs and sulfated GAGs in the interstitium of skin biopsies (43). The more negative charge carried by sulfated GAG component of proteoglycans compared to hyaluronan enhances the ability of these matrix components to bind Na^+ (44).

These findings indicate that an active regulatory mechanism responds to long-term high dietary salt by increasing the total GAG content of skin including a relative increase in the strongly negatively charged sulfated GAGs thus enhancing the ability of the skin to act a reservoir for non-osmotic storage of Na^+. Interestingly, when challenged with a high-salt diet, rats prone to salt-sensitive hypertension show a reduced ability to store Na^+ non-osmotically compared to control rats (45).

In addition to the changes in interstitial GAG content, high dietary salt in rats also leads to interstitial infiltration of immune cells of the mononuclear phagocyte system (MPS) including macrophages and to lymphatic capillary hyperplasia in skin with enhanced clearance of sodium and chloride (46, 47). The MPS cells appear to play a regulatory role in this process. High interstitial salt concentrations activate the tonicity-responsive enhancer-binding protein transcription factor in MPS cells leading to secretion of vascular endothelial growth factor-C, a promoter of lymphangiogenesis and lymphatic hyperplasia (46). The high salt diet also leads to a modest, but measurable, increase in arterial blood pressure. Depletion of MPS cells blocks this response to high salt intake and increases its hypertensive effect. A subsequent study demonstrated that pretreatment with an inhibitor of vascular endothelial growth factor exaggerated the hypertensive effect of a high salt diet in rats but did not inhibit the lymphatic hyperplasia in skin (48). Therefore, while the interstitial space of the skin clearly plays an important role in sodium and water balance and long-term regulation of blood pressure, the role of dermal lymphatic development in this regulatory process remains unclear.

THE LYMPH SYSTEM AND LYMPHATIC DRAINAGE

The lymphatic system drains interstitial fluid first through blind-end initial lymphatic capillaries located within the interstitial space (49). With diameters up to 100 μm, these lymphatic capillaries are larger than blood capillaries and contain no mural smooth muscle. This fluid, now called lymph, is transported to larger collecting lymphatic vessels that contain smooth muscle and regularly spaced unidirectional valves. Lymph continues to flow through progressively larger vessels such as the thoracic duct and right lymphatic duct and, then, empties into the blood circulation at the great veins of the neck.

Collecting lymphatic vessels contract spontaneously and are capable of driving flow against an axial pressure gradient.

The pumping activity of these lymphatic vessels has been demonstrated to respond to mechanical stimuli and to numerous vasoactive mediators (50–53). In response to increased luminal pressure (hoop stress), these contractile lymphatics increase the strength and frequency of contraction (50). While, in response to increased luminal flow (shear stress), they dilate and decrease their contraction frequency (52).

Lymph flow through the intact lymphatic network has been modeled using the Drake-Laine equation

$$J_L = (P_{int} + P_p - SVP)/R_L$$

in which J_L is lymph flow, P_{int} is the interstitial fluid pressure, P_p is the effective driving pressure contributed by the intrinsic pumping activity of lymphatic vessels and extrinsic compression, SVP is the systemic venous pressure to which the lymph is flowing and R_L is the effective resistance to flow offered by the lymphatic network (54). The driving pressure provided by lymphatic pumping explains why tissues such as skin and lung can have subatmospheric interstitial fluid pressure and why lymph flows from that low-pressure region to the higher-pressure veins. The "effective" lymphatic resistance (R_L) in the Drake-Laine equation was derived from the slope of the flow-outflow pressure relationship in a multi-branched system of cyclically contracting lymphatic vessels (54). Therefore, rather than being a simple measure of the hydraulic resistance of a tube, it is one measure of the behavior of a complex system. This suggests that its value can be affected by many factors including lymphatic contractility and contraction rate as well as interactions between lymphatic vessels.

Increases in interstitial fluid pressure, which is the upstream pressure for the lymphatic system, have been shown to dramatically increase lymph flow following increases in microvascular filtration in the affected organ. In rat experiments, intravenous administration of 0.9% NaCl solution at a rate of 0.2 $ml \cdot min^{-1} \cdot 100\,g$ body wt^{-1} for 45 min resulted in a 25-fold increase in measured flow from the main intestinal lymph trunk (55). Interestingly, the increase in lymph flow calculated from dimensional changes in mesenteric lymphatic vessels and the contraction frequency was closer to a 2.5-fold increase. A likely explanation for this large discrepancy is that, under conditions of marked increases in P_{int}, the resulting increase in lymph flow is the result of enhanced *passive* flow rather than increased lymphatic pumping. This is because, when upstream (interstitial) pressure exceeds downstream (venous) pressure, the passive flow generated outstrips the pumping capacity of the lymphatic vessel (56). In fact, under these conditions, stimulation of lymphatic contractile activity reduces, rather than augments, flow (57). This observation illustrates the counterintuitive physiologic utility of lymphatic vessel relaxation in response to increased shear stress since dilation and reduced pumping activity under high flow conditions will increase flow.

Venous pressure exerts two opposing effects on lymph flow. First, increased venous pressure leads to sequential increases in microvascular fluid pressure, microvascular filtration and interstitial pressure, thus enhancing lymph flow. Second, as seen in the Drake-Laine equation, systemic venous hypertension can reduce lymph flow by elevating lymphatic outflow pressure (58–60). In experimental studies, the effect of increasing lymphatic outflow pressure is exaggerated in anesthetized animals likely because the anesthetic agent reduces lymphatic contractility (61). In unanesthetized animals, elevation of systemic venous pressure has only a modest effect on lymph flow because the increase in lymphatic luminal pressure elicits a hoop stress-mediated increase in the strength and frequency of lymphatic pumping (60, 62). However, when it occurs in conjunction with any additional edemagenic challenge such as increased microvascular pressure, systemic venous hypertension significantly worsens edema formation (58).

The influence of lymphatic outflow pressure is also discernible in interactions within the lymphatic system. Lymph from both the intestine and the liver flows into the cisterna chyli prior to entering the thoracic duct. The capacity for the intestine to drive lymph flow against increased outflow pressure is less than that of the liver (63, 64). Therefore, increases in thoracic duct pressure induce a more pronounced reduction in mesenteric vs. hepatic lymph flow (63). In a canine model of caudal vena caval hypertension, increased lymph flow from the liver contributed to increased cisternal pressure and, thereby, reduced lymph flow from the intestine and exacerbated intestinal edema and ascites formation (64).

Lymphatic vessels not only respond acutely to changes in lymph flow and pressure, but also adapt chronically in response to mechanical stimuli. Vessels exposed to prolonged increases in luminal pressure respond within a few days by increasing pumping capacity (65). This adaptation carries the benefit of promoting active lymphatic pumping in response to a downstream obstruction or increase in outflow pressure. Conversely, a vessel exposed to high lymph flow due to increased microvascular filtration responds by becoming a weaker pump (66). This is also a beneficial change that would boost passive lymph flow in response to edema formation and increased interstitial fluid pressure.

INTESTINAL INTERSTITIUM AND MESENTERIC LYMPH IN TRAUMA/HEMORRHAGIC SHOCK

Diminished blood flow to the gastrointestinal tract resulting from trauma/hemorrhagic shock plays a key role in the subsequent development of systemic inflammatory response syndrome (SIRS) including acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) (67, 68). An early view that intestinal injury allowed entry of enteric bacteria and endotoxin into the intestinal interstitial space and, from there, into the mesenteric circulation was not well-supported by later studies (67–69).

An alternative hypothesis proposes that transit *via* the mesenteric lymphatic system allows proinflammatory agents to travel from the intestinal interstitial space to the general circulation bypassing the portal vein and liver. In 1970, Glenn and Lefer reported that diversion of thoracic duct lymph improved survival in a model of hemorrhagic shock (70).

Later studies by Deitch et al. (71) focused on the intestinal interstitial space and its lymphatic drainage by demonstrating that while mesenteric lymph from a hemorrhagic shock model in rats was cytotoxic, portal vein plasma was not (71–73). In addition, when mesenteric lymph is prevented from entering the circulation, shock-induced injury to lung and heart is avoided and survival is enhanced (71, 74). Models of intestinal ischemia/reperfusion rather than hypovolemic shock showed similar results. Mesenteric lymph collected following intestinal hypoperfusion and, then, administered intravenously to clinically normal animals provokes tissue injury affecting the lungs and heart (75–77). Similarly, the myocardial edema induced in a canine model of mesenteric ischemia/reperfusion is eliminated by diversion of mesenteric lymph (75).

Mesenteric lymph also appears to play a central role in the pathogenesis of multiple organ failure associated with dermal burn injury (78). Ligation of the mesenteric lymphatic duct prevents cardiac dysfunction in rats with experimental burn injury (79). Interestingly, electrical stimulation of the vagus nerve increases intestinal tight junction proteins (i.e., occludins) in adjacent cells thereby protecting against intestinal barrier injury and peritoneal inflammatory response following dermal burn injury (80, 81).

Vagal nerve stimulation also increases intestinal blood flow, prevents intestinal barrier dysfunction, markedly decreases lung inflammation and inhibits development of inflammatory and cytotoxic activity in mesenteric lymph subsequent to hemorrhagic shock (82–86). As a therapeutic modality, vagal nerve stimulation is currently impractical. However, a pharmacologic vagal agonist, CPSI-121, also prevents intestinal injury and acute lung injury as well as attenuates development of inflammatory activity in mesenteric lymph following induction of hemorrhagic shock (87, 88).

The nature of the cytotoxic element in the affected mesenteric lymph has been addressed by several investigations focused on the entry of bacteria and endotoxin from the GI tract and activation of endogenous proinflammatory mediators (68). The hypothesis with the strongest current evidentiary support involves passage of pancreatic digestive enzymes through a damaged intestinal mucosa into the interstitial space. Mitsuoka et al. (89) demonstrated that luminal dilution and inhibition of digestive pancreatic enzymes diminished the lung injury induced by intestinal ischemia/reperfusion. Subsequently, they and others have provided evidence that intestinal hypoperfusion and ischemia/reperfusion injury lead to mucosal barrier disruption and entry of luminal components including free fatty acids and digestive enzymes from the exocrine pancreas into the intestinal interstitium (90–92). Once there, the pancreatic enzymes begin to digest interstitial components to produce novel inflammatory and cytotoxic agents such as unbound free fatty acids (93). These pancreatic enzymes and cytotoxic agents can then gain access to the general circulation *via* the mesenteric lymphatics as well as by the portal circulation and peritoneal cavity (71, 74, 94). Interruption of this pathologic cascade leads to more positive outcomes. Intraluminal administration of a protease inhibitor and a gastric and pancreatic lipase inhibitor reduces intestinal tissue injury and improves cardiovascular function (95). In addition, blockade of pancreatic enzymes within the bowel lumen increases survival in three forms of experimental shock caused by hemorrhage, septic peritonitis and intravenous endotoxin (96). Three different protease inhibitors instilled directly into the small intestine 1 h after initiation of the shock episode were all shown to have a beneficial effect (96).

SEROSAL TRANSUDATION

Transudation or fluid filtration through the serosal covering of organs positioned within the pericardial, pleural and peritoneal spaces provides a second route for interstitial fluid removal in healthy organs. The factors governing filtration across the serosal barrier are approximated by a modified form of the Starling-Landis equation where interstitial fluid pressure acts to drive fluid flow out of the organ and interstitial COP acts to restrain that flow (97, 98). In both the heart and liver, increases in venous and microvascular pressures result in increases in interstitial fluid pressure and, thus, serosal transudation (97, 98). These findings are consistent with the clinical observations of pericardial effusion and ascites associated with pulmonary hypertension and right-sided heart disease (99–101).

In response to chronic edemagenic challenges, the permeability of the serosal surface can change over time. Following 5–6 weeks of caudal vena caval hypertension in dogs, the fluid and protein permeabilities of the hepatic serosal surface significantly decreased leading to significant decreases in serosal transudation and ascites volume (27).

EDEMA: CAUSES, MECHANISMS, AND CONSEQUENCES

Interstitial edema, the accumulation of excess fluid in the interstitial space, can lead to a number of negative consequences depending on the organ system involved. In addition to increasing oxygen diffusion distance within tissues, edema affecting the lung, heart and intestine impairs the organ's mechanical and physiological function (102–104). Interstitial edema in organs like the brain, intestines and kidney, where volume expansion is constrained, can lead to the development of compartment syndrome with resultant impairment of blood flow and organ failure (105). For the same reason, intestinal edema can also prevent surgical closure of an open abdomen. Pulmonary edema increases the work of breathing and carries the added risk of alveolar flooding.

Classically, interstitial edema forms as a result of some combination of increased microvascular pressure, decreased plasma COP, increased microvascular permeability and decreased lymphatic drainage. The effect of the first three of these factors is to increase the rate of microvascular filtration into the interstitial space as can be appreciated in the Starling-Landis equation (1). As discussed above, inhibition of lymphatic drainage caused by lymphatic obstruction or elevated lymphatic outflow pressure does not necessarily promote interstitial edema formation. However, it does magnify the impact of other

edemagenic insults such as elevated microvascular pressure (58, 106).

Microvascular fluid pressure acts to promote microvascular filtration and is commonly increased in association with venous hypertension resulting from venous thrombosis or cardiac dysfunction. It is also increased by the arteriolar dilation that occurs in maldistributive shock associated with inflammation and sepsis. Plasma COP opposes microvascular fluid pressure and acts to restrain filtration, therefore decreased plasma COP due to hypoproteinemia/hypoalbuminemia also leads to greater filtration. This increase in filtration can have a broader impact than the easily recognized effects on lungs and skin. Hypoproteinemia in dogs has been shown to cause myocardial edema and impaired diastolic function (107). Intravenous administration of isotonic crystalloid solutions to normal subjects thus promotes interstitial edema formation by simultaneously increasing microvascular pressure *via* blood volume expansion and decreasing plasma colloid osmotic pressure *via* dilution.

Microvascular filtration can also be increased as a result of increases in the permeability of the microvascular barrier to either fluid or protein (1, 108–110). The permeability of the microvascular barrier to both is actively regulated at the level of the vascular endothelium and the glycocalyx layer located on the endothelial surface (111, 112). Numerous inflammatory mediators increase microvascular permeability leading to increased microvascular filtration and interstitial edema formation (111, 112).

Inflammatory and Immune-Mediated Edema Formation

Changes in microvascular pressure and microvascular permeability are not the only and, perhaps, not even the most important causes of interstitial edema during inflammation. The standard view of microvascular filtration assumes that the interstitial fluid pressure is relatively stable and that it changes in a predictable fashion as interstitial volume increases and decreases. However, a series of experiments at the University of Bergen investigating inflammatory and immune-mediated alterations in the skin and tracheal mucosa of rats has revealed that interstitial pressure can fall precipitously thereby strongly promoting microvascular filtration and inducing a rapid increase in interstitial volume (7, 19).

Studies exploring these phenomena have taken one of two basic forms. Experiments that allow continued microvascular filtration following the inflammatory insult show an initial modest fall in interstitial fluid pressure followed by a return to near baseline values accompanied by a rapid increase in interstitial volume. In contrast, experiments that actively minimize microvascular filtration at the onset of the insult often show a profound fall in interstitial fluid pressure. These findings indicate a fundamental shift in the interstitial pressure-volume relationship (see **Figure 1**). Following dermal burn injuries in rats with continued filtration, intradermal interstitial fluid pressure fell from −1 to −31 mmHg within 15 min and, then, rose to approximately atmospheric pressure as edema developed (113). The same insult induced in rats immediately following euthanasia, thus limiting microvascular filtration, caused mean interstitial pressure to fall to −135 mmHg. Non-injured skin in these experiments showed no change in interstitial pressure.

Similar decreases in interstitial fluid pressure, although generally not as dramatic, have been induced in skin following local injection of numerous proinflammatory stimuli including PGE_1, PGI_2, histamine, cytochalasin D, xylene, carrageenan, TNF-α, IL-1β, and IL-6 (114–119). Ischemia-reperfusion injury and freezing injury have also been demonstrated to significantly lower interstitial fluid pressure and promote edema formation in skin (120, 121).

Edema formation associated with immune-mediated phenomena shows similar changes in interstitial fluid pressure. In a model of dextran anaphylaxis in rats, dermal interstitial pressure fell 5–10 mmHg in 20–40 min when circulatory arrest was induced 1 min following intravenous dextran administration (115, 122). In the absence of circulatory arrest, visible edema formed with no significant change in interstitial fluid pressure.

Inflammatory/immune-mediated challenges similar to those previously described also induce edema in tracheal mucosa associated with decreases in interstitial fluid pressure. Like skin, dextran anaphylaxis in rats was characterized by more negative interstitial pressure and rapid edema formation in the tracheal mucosa (122, 123). Tracheal interstitial pressure is also lowered by agents that induce mast cell degranulation (C48/80 and polymyxin B sulfate) as well as by stimulation of vagal nerve C fibers (124, 125).

Integrins, transmembrane proteins that facilitate fibroblast adhesion to the extracellular matrix, appear to play a central role in the inflammation-related fall in interstitial pressure (25). Subdermal injection of anti-β1 integrin IgG in rats with circulatory arrest caused a concentration-dependent decrease in interstitial fluid pressure of 4–6 mmHg in 10 min compared to preimmune IgG from the same source (126). In rats with intact circulation, anti-β1 integrin IgG caused interstitial volume to increase significantly within the same time frame. In those same studies, injection of anti-fibronectin IgG had no measurable effect on interstitial fluid pressure. In a subsequent study, intravenous administration of the anti-inflammatory agent, α-trinositol, had no effect on interstitial fluid pressure when used alone, but prevented the decrease in interstitial fluid pressure caused by subdermal administration of anti-β1 integrin IgG (127). Similarly, the ability of anti-α2β1 integrin IgG and anti-β1 integrin IgG to lower interstitial pressure in rat dermis was eliminated by simultaneous subdermal administration of platelet-derived growth factor-BB (PDGF-BB) (128). PDGF-BB exerts this effect by upregulating the expression of β3 integrin even though blockade of β3 integrin does not lower interstitial pressure (129). The investigators propose that normal tension within the extracellular matrix is maintained by β1 integrin-mediated contraction, that proinflammatory mediators disrupt the β1-integrin connections allowing rapid edema formation and that PDGF-BB re-establishes tension within the matrix and counteracts edema by stimulating the activity of β3-integrin (7).

In addition to its ability to counteract the effects of anti-β1 integrin IgG, pre-treatment with α-trinositol has been shown

to eliminate or markedly attenuate the decrease in interstitial fluid pressure in skin and trachea in response to burn injury, freezing injury, subdermal injection of carrageenan and dextran anaphylaxis (120, 122, 130, 131). α-trinositol appears to have a modest ability to reduce edema formation when administered after, rather than before, the tissue insult. PDGF-BB, on the other hand, can normalize interstitial fluid pressure when administered 10–30 min following the insult (128, 129). In addition to α-trinositol and PDGF-BB, agents shown to prevent or reverse the fall in interstitial pressure include prostaglandin $F_2\alpha$, corticotropin releasing factor, insulin and vitamin C (117, 132–134).

This inflammatory/immune-mediated decrease in interstitial fluid pressure has a dramatic effect on microvascular filtration. Reed and Rodt calculated that appearance of visible edema within 10–20 min of the insult characteristic of inflammatory processes indicated a 50–100-fold increase in microvascular filtration rate (115). Although microvascular permeability increases during inflammation, the observed doubling or tripling of the capillary filtration coefficient is not sufficient to explain such a rapid increase in interstitial volume (25). The normal net filtration pressure, i.e., the combined hydrostatic and colloid osmotic pressure gradients, is 0.5–1 mmHg in peripheral tissues (25). The rapid fall in interstitial pressure during the early inflammatory response suggests a 10–100-fold increase in the net filtration pressure. This coincides closely with an early report by Arturson and Mellander in which they calculated an increase in the net filtration pressure following dermal burns of 250–300 mmHg (135). Together, these data strongly suggest that increased negativity of interstitial fluid pressure is the dominant factor in the generation of inflammatory and immune-mediated interstitial edema in loose connective tissue.

ANTI-EDEMA MECHANISMS AND MEDICATIONS

When interstitial edema begins to form, its formation is opposed by a set of mechanisms that act to moderate the magnitude of the interstitial volume increase. These mechanisms are automatic, interdependent and intrinsic to the tissue; however, their effectiveness is not without limit. The result is that the impact of the initial cause of the edema is often muted by the anti-edema mechanisms, but the impact of additional insults can be pronounced. For example, a hypoalbuminemic patient may not display clinically apparent edema, however subsequent administration of intravenous fluids may induce profound edema formation.

Following an increase in the microvascular filtration rate caused by increased venous and microvascular pressures, most organs exhibit four anti-edema responses: (1) an increase in interstitial fluid pressure, (2) a decrease in interstitial COP resulting from protein washdown, (3) an increase in lymph flow, and (4) an increase in trans-serosal flow in organs located within potential spaces. The increase in interstitial fluid pressure and the decrease in COP both act to reduce microvascular filtration according to the relationships modeled in the Starling-Landis equation. The impact of protein washdown as an anti-edema mechanism is blunted by the fact that larger protein molecules washdown to a greater degree than smaller protein species such as albumin. This changes the relationship between protein concentration and COP such that, even at a lower protein concentration (measured as mass per unit volume), there is still a large number of small protein molecules in the interstitial space exerting a considerable COP (136).

Increased lymph flow and serosal transudation provide enhanced removal of interstitial fluid. Because the microlymphatics provide no significant barrier to protein movement (49), lymphatic drainage is more effective than trans-serosal flow at removing protein from the interstitial space; however, this observation is organ dependent. For example, the epicardium is much less permeable to protein than the hepatic serosal surface. Therefore, interstitial protein removal in the heart is more dependent on lymphatic drainage than in the liver (97, 98). This means that serosal transudation in such organs is not independent of lymphatic function. The low serosal protein permeability in organs such as the heart leads to an interesting dynamic in which obstruction of lymphatic drainage causes an increase in interstitial protein concentration and, therefore, a decrease in serosal fluid transudation (29, 97).

Intravenous administration of plasma substitutes containing colloids such as albumin, fresh frozen plasma, dextran or hydroxyethyl starch have been advocated in the treatment of hypovolemia. Their use was encouraged on the supposition that, compared to crystalloid solutions, increases in plasma colloid osmotic pressure would reduce the redistribution of administered fluid to the interstitial space and, thus, maximize the increase in circulating volume. This would improve clinical management of hypovolemia by providing circulatory support while minimizing interstitial edema formation. Unfortunately, several meta-analyses of numerous clinical trials comparing colloid and crystalloid therapy in critically ill humans have failed to demonstrate an improvement in mortality attributable to colloid use (137–139). In addition, the use of some colloids carries an increased risk of negative consequences. Hydroxyethyl starch accumulates in multiple tissues and remains for prolonged periods and, in human trials, its use is correlated with an increased need for renal replacement (140).

These analyses do not provide an explanation for why colloids do not result in an improvement in mortality; however, one reason could be that the fundamental premise supporting their use is flawed. As early as 1987, Michel and Phillips demonstrated that, in single capillaries, lowering of capillary hydrostatic pressure did not lead to steady-state fluid reabsorption into the capillary (141). Rather, as capillary pressure falls, outward filtration falls and then stabilizes at very low, but positive, levels. This coincides with the earlier discussion of the limits of transcapillary refill. When capillary pressure falls, interstitial hydrostatic pressure falls and interstitial COP increases thus preventing steady-state reabsorption. This observation was emphasized recently to point out that steady-state fluid reabsorption does not occur in the vast majority of capillary beds (1). However, another way to look at this

phenomenon is that, at the low capillary pressures characteristic of hypovolemia, changes in capillary pressure have little effect on microvascular filtration. This suggests that fluid replacement in hypovolemic patients would not initially increase filtration and, therefore, would not predispose to interstitial edema formation (142). Early in the course of therapy, most of the administered solution would remain in the plasma space regardless of whether it was colloid or crystalloid. An excellent review of the impact of our current understanding of microvascular filtration on intravenous fluid therapy considerations is available (142).

Crystalloid solutions are not considered useful as a treatment for interstitial edema because, in most tissues, the microvascular barrier is freely permeable to sodium and chloride ions. Thus, these ions are unable to generate an osmotic pressure gradient necessary to promote water movement. Therefore, it is surprising that intravenous hypertonic saline appears to be effective in the prevention of experimental hydrostatically-induced intestinal edema (143). In rat experiments using mesenteric venous hypertension and intravenous isotonic saline infusion over a 7-h period to create intestinal edema, the addition of 7.5% intravenous saline solution (4 mL/kg) to the protocol resulted in decreased intestinal wall fluid volume, increased peritoneal and luminal fluid volumes and increased urine output (144). The hydraulic conductivity across the intestinal seromuscular layer was significantly increased in the hypertonic saline group which could explain fluid movement from the interstitium to the peritoneal space. Western blot analysis of the intestinal tissue demonstrated increased expression of aquaporin 4 protein levels in the hypertonic saline group suggesting a possible mechanism for the change in hydraulic conductivity.

FUTURE DIRECTIONS

New appreciation of the interstitial space as a site of active regulation and potentially rapid change invites a host of questions regarding clinical impact—questions that may not be answered by current lines of research.

Investigations into the role of the extracellular matrix in the regulation of salt and water balance presently focus on the connection to hypertension. While this is certainly an important issue, particularly for human medicine, it is not the only one. The impact of changes in the skin content of sulfated GAGs on interstitial mechanics is unknown. One could hypothesize that, if an increase in interstitial GAG content induced by a high salt diet were to decrease interstitial compliance, the transcapillary refill that occurs during hemorrhage might be blunted leaving the subject more susceptible to hemorrhagic shock. First, of course, the effect of dietary salt on the extracellular matrix composition needs to be demonstrated in veterinary patients.

The idea that the rapid edema formation associated with inflammation and immune phenomena is caused, in large part, by a fall in interstitial fluid pressure runs counter to previous expectation. The interstitial changes that characterize this process have been studied in skin and tracheal mucosa, in part, because those tissues provide *in vivo* preparations that are stable enough to allow precise measures of interstitial fluid pressure. Loose connective tissue, however, is found throughout the body. It seems likely, therefore, that inflammatory edema formation affecting other tissues, such as the intestines or lung, involves a similar mechanism. It might even be that the lamellar edema that occurs in horses suffering from laminitis occurs initially because of a fall in interstitial fluid pressure in the lamellar dermis.

Published reports offer some hope for finding effective therapies for inflammation-induced edema and shock. PDGF-BB, insulin and α-trinositol have all been shown experimentally to moderate or reverse the fall in interstitial fluid pressure and interstitial edema formation when administered post-treatment, as well as pre-treatment, for inflammatory edema (120, 122, 131, 134). The ability to effectively intervene after the onset of the disease state makes the use of these agents or their analogs more clinically feasible. Studies demonstrating that pancreatic enzyme dilution and inhibition as well as administration of vagal agonists improve outcomes when used to treat circulatory shock-related organ dysfunction also provide new avenues for clinical investigation. Also, since the pathogenesis of inflammatory edema likely overlaps with the pathogenesis of shock-induced intestinal ischemia-reperfusion, there will likely be effective common therapeutic approaches for these conditions.

Human clinical trials suggest a benefit to the use of intravenous hypertonic saline in edematous patients based on it being used as a *replacement* for isotonic solutions (145). This benefit is believed due to the reduced administered volume and the avoidance of fluid overload when compared to isotonic solutions. However, experimental studies in rats demonstrate an ability to reduce intestinal edema formation when hypertonic saline is used *in addition* to isotonic solutions (143, 144, 146). Therefore, the observed benefit in these studies cannot be attributed to a reduction in the volume of intravenous solutions administered. Proposed mechanisms for this additional benefit include aquaporin-mediated changes in tissue permeability leading to fluid shifts as well as modulation of trauma-induced inflammatory and immune processes (144, 147, 148).

AUTHOR CONTRIBUTIONS

RS was responsible for all stages of authorship including research and writing.

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REVIEW
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Advances in the Starling Principle and Microvascular Fluid Exchange; Consequences and Implications for Fluid Therapy

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Ernest Starling first presented a hypothesis about the absorption of tissue fluid to the plasma within tissue capillaries in 1896. In this Chapter we trace the evolution of Starling's hypothesis to a principle and an equation, and then look in more detail at the extension of the Starling principle in recent years. In 2012 Thomas Woodcock and his son proposed that experience and experimental observations surrounding clinical practices involving the administration of intravenous fluids were better explained by the revised Starling principle. In particular, the revised or extended Starling principle can explain why crystalloid resuscitation from the abrupt physiologic insult of hypovolaemia is much more effective than the pre-revision Starling principle had led clinicians to expect. The authors of this chapter have since combined their science and clinical expertise to offer clinicians a better basis for their practice of rational fluid therapy.

Keywords: resuscitation, crystalloid and colloid infusion, hypoalbuminaemia, fluid therapy, oedema (edema), starling principle, glycocalyx model

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INTRODUCTION

Hippocrates and Aristotle made reference to lymphatic vessels more than 2,000 years ago, and the Greek physician Galen had observed mesenteric chyle in his dissections of living animals in the second century AD. Gasparo Aselli was the Italian anatomist (1581–1626) whose studies on living dogs in 1622 rediscovered the appearance of mesenteric lacteals (milky veins) after feeding. Aselli's glands are para-aortic lymph nodes near the pancreas of mammals. Danish physician Thomas Bartholin and Olaus Rudbeck, who was Professor of Anatomy, Biology and Physics at Uppsala University in Sweden published the first full description of human lymphatics in 1652. Bartholin named the vessels he observed vasae lymphaticae, while in Sweden Olauf Rudbeck had made unpublished presentations on his own discovery. In mid-century Britain, William Hewson observed the rhythmic contraction of lymphatic vessels and William Hunter proposed that the purpose of the lymphatic system is to absorb tissue fluids for return to the blood circulation (1–3). The work of Ernest Starling in late-nineteenth century London gave us an appreciation of the Starling forces that result in the formation of extracellular fluid and lymph by capillary filtration from the plasma of circulating blood. Starling not only confirmed that raising microvascular pressures increased interstitial fluid formation, as indicated by Ludwig & Noll, (4) but also demonstrated in perfused hind limbs of anesthetized dogs that saline solution injected into the tissues could be absorbed directly into the blood, whereas injections of plasma into the tissues could

not be absorbed (5). He suggested the balance of hydrostatic and colloid osmotic pressures across microvascular (i.e., capillary and venular) walls was responsible not only for the partitioning of fluid between plasma and tissues but also for rapid adjustments of blood volume. Starling reviewed his work and its implications in Schafer's Textbook and suggested the general role of the lymphatics was to clear excess fluid remaining in the tissues. In his conclusion, he noted that since the hydrostatic pressure at the arterial end of capillaries was greater than that at the venous end, fluid might be filtered from plasma to tissues at the arterial end and reabsorbed at the venous end (1). This picture was soon adopted and continued to be used for the next 100 years as a popular way of teaching Starling's Hypothesis. There is no reproducible experimental evidence for this picture and the recognition that microvascular walls are permeable to plasma proteins means a picture of this kind could only exist transiently. Until recently standard textbooks presented the lymphatics as an accessory route through which fluid can flow from the interstitial spaces into the blood (6). Levick's Introduction to Cardiovascular Physiology 6e dismisses this concept as "still taught tenaciously… yet clearly disproved by a large body of evidence over the past 20 years." (7) Tissue fluid balance in most tissues critically depends on lymphatic function. In this chapter we introduce the twenty-first century view of Starling forces and the vital circulations of extracellular fluids pumped by the lymphatic system.

Starling Forces

We start from Starling's classic experiments on dogs, published in 1896 (4). In one experiment he created 'artificial oedema' with 1% Sodium Chloride solution injected into the hind leg of a freshly-killed dog. The result enabled him to "affirm with certainty that isotonic salt solutions can be taken up directly by the blood circulating in the blood vessels." This fundamental physiological principle is unquestioned to this day and relied upon when fluids are administered subcutaneously in small animal veterinary practice.

More than a half century later, Staverman (8) suggested that osmotic pressures exerted by solutions across membranes which were permeable to solutes, could be better understood in terms of Onsager's theory of irreversible thermodynamics. Onsager's theory predicted that flows of solvent (water) and solute through the membrane should interact, modifying the forces maintaining the process (i.e. the forces being the differences in hydrostatic and osmotic pressures across the membrane). Thus, the effective osmotic pressure difference exerted by solutions at different concentrations across a leaky membrane would be less than that exerted by the same solutions across a perfect semi-permeable membrane by a factor, σ. A perfect semi-permeable membrane is one that is permeable to the solvent (water) yet completely impermeable to the solute. The fraction of solute carried by the solvent through a leaky membrane during ultrafiltration was the complement of σ that is (1-σ). The value of σ varies between 0 and 1.0, where σ =1 describes a perfectly semi-permeable membrane and σ = 0 indicates a membrane which hinders the passage of solute through it no more than the passage of water. This concept was developed and applied to biological membranes by Kedem and Katchalsky (9) who discussed the osmotic pressures exerted by small molecules across microvascular walls in an attempt to measure concentration differences for small solutes. Kedem & Katchalsky's equation for fluid flow across biological membranes is what we know as the Starling equation. For fluid exchange across microvascular walls it is written as:

$$J_V = K\,(\Delta P - \sigma\Delta\Pi)\,. \tag{1}$$

Here, J_V is the fluid filtration rate (ml.min^{-1}); ΔP is the hydrostatic pressure difference across microvascular walls, $\Delta\Pi$ the colloid osmotic pressure difference and σ is Staverman's reflection coefficient. Strictly speaking the colloid osmotic pressure of plasma, $\sigma\Delta\Pi$ is the summation of the products of all the plasma solutes contributing to the total osmotic pressure difference across microvascular walls, that is, $\sum_n \sigma\Delta\Pi$. Because the reflection coefficients of the small solutes are low (<0.1) and their concentration differences across microvascular walls negligible, the colloid osmotic pressure is the osmotic pressure exerted across microvascular walls by plasma macromolecules.

The constant, K, as used here, is the hydraulic conductance of microvascular walls to fluid and is dependent on both their permeability coefficient and their surface area for filtration. In many tissues, the area for fluid exchange can be rapidly varied by vasomotor reflexes. Woodcock proposes that clinicians may find it easier to think of conductance (or conductivity or permeability) of a capillary wall to the passage of solvent as a transendothelial resistance (10). To be precise, trans-endothelial resistance is the inverse of the product of hydraulic conductivity Lp and endothelial surface area A through which flow is occurring, that is, (1/LpA) rather than (1/Lp).

The Starling equation remains valid today (11). Tissue fluid balance, plasma volume regulation and clinical oedema formation are governed by the Starling principle of microvascular fluid exchange. The classical Starling hypothesis assumed that σ = 1, since Starling believed microvascular walls were completely impermeable to plasma proteins. Consider as an example the blood-brain barrier which is almost impermeable to both small molecules and large molecules, expressed in the reflection coefficient σ for mannitol and the reflection coefficient σ for albumin being close to 1. Clinicians could therefore use intra-vascular injection of a solution as an osmotic diuretic to reduce brain oedema. By contrast, the microvasculature of the sinusoidal tissues poses little or no restriction on the movement of smaller or larger molecules, and reflection coefficients here approach zero. Fluid exchange depends on hydrostatic pressure differences.

Mean Capillary Pressure

The axial capillary pressure gradient and the mean capillary pressure are determined by the local arterial and venous pressures and the ratio of the capillary inflow (arteriolar) resistance to the capillary outflow (venular) resistance (12). This means that if the arterial pressure and blood flow are raised (e.g., by increased cardiac output) then providing the local inflow and outflow resistances are unchanged, the mean capillary pressure is raised also. Similarly, if resistances are unchanged and the arterial pressure is lowered, capillary pressure will fall. In the systemic circulation, however, tissue blood flow is continually

adjusted by cardiovascular reflexes and local mechanical and chemical responses to ensure tissue oxygenation is adequate. Cardiovascular reflexes maintaining mean arterial pressure may increase arteriolar resistance to resting skeletal muscle reducing the tissue blood flow and lowering mean capillary pressure while arterial pressure is increased. Detailed investigations into the response and their effects on net fluid exchange were explored by Folkow and his colleagues in the 1960s (13, 14). An interesting comparison between the responses of cats and humans is reported by Mellander et al. (15).

Intravascular hypervolaemia causes capillary hypertension, while hypovolaemia causes capillary hypotension. Indeed, the compensatory arteriolar constriction that accompanies hypovolaemia amplifies the associated capillary hypotension. It is important to realize that the vasodilation of systemic inflammatory response has the effect of simultaneously lowering the arterial blood pressure and raising the mean capillary pressure.

Extravascular colloid osmotic pressure is the second filtration-driving Starling force. Techniques were developed during the twentieth century to sample interstitial fluid and to measure interstitial colloid osmotic pressure *in-vivo*. π_i was found to be greater than earlier workers had believed. Levick (16) reviewed data from a range of different tissues in mammals, including humans, in 1991 and showed that the Starling equation predicted levels of filtration into the tissues that were many times greater than could be consistent with lymph flow from the tissues, even if the microvascular pressure were equal to the venous pressure.

It is now recognized that the luminal endothelial glycocalyx is the molecular filter of both continuous and fenestrated endothelia and may contribute as much as half of the hydraulic resistance to flow to the intact microvascular wall (17, 18). Filtered fluid leaving the glycocalyx creates a subdomain of the interstitial fluid with a lower colloid osmotic pressure than that of the average interstitial fluid. This subdomain is the sub-glycocalyx space. Solvent filtered by the glycocalyx of continuous endothelia is channeled into the intercellular clefts and through occasional breaks in the tight junction. The velocity of solvent flow through these inter-endothelial channels is very high and the volume contained within this subdomain is very small. Calculations by Michel (19) and Weinbaum (20) revealed that even when the total pressure difference across the microvascular wall was as little as 1 cm H_2_O, the filtration velocity through the channels would prevent back diffusion of macromolecules into the sub-glycocalyx space from the main interstitial space. Consequently, the colloid osmotic pressure of fluid immediately beyond the endothelial glycocalyx layer (in the subglycocalyx space) is less than the general interstitial fluid because macromolecules are largely excluded by the glycocalyx, and varies inversely with the transendothelial filtration rate. Most plasma macromolecules cross microvascular walls through openings in the glycocalyx leading to trans-endothelial channels or transcytotic vesicles that discharge their contents to the interstitium (21–25). The colloid osmotic pressure of fluid in the subglycocalyx space is reduced at high filtration rates and increases when filtration rate falls. While it has been recognized for over 60 years that the main pathway for macromolecules was separate from that for water and small hydrophilic solutes, it was 30 years before it's implication for fluid exchange was recognized. This was first proposed to account for the large discrepancies between the lymph flow and the steady state values of Starling forces of various tissues estimated from the mean colloid osmotic pressure of the interstitial fluid demonstrated by Levick (16). This concept, the Michel–Weinbaum model or glycocalyx model, and the associated hockey stick or *J* curve, are discussed in more detail below.

The ***colloid osmotic pressure of plasma*** π_p is the major absorptive force. It is readily measurable, though clinicians tend to focus on the plasma albumin concentration as a surrogate (26). There are some misconceptions about albumin and its role in Starling forces. It is correctly taught that plasma albumin accounts for most of the plasma colloid osmotic pressure in most healthy individuals. This is true as albumin accounts for 65% of plasma colloid osmotic pressure but the globulins contribute a not insignificant 35%. Further, there are rare examples of healthy and apparently non-oedematous individuals who are congenitally analbuminaemic. Hypoalbuminaemia is a common finding in critical illness, but is not invariably accompanied by reduced plasma colloid osmotic pressure (27). More importantly, clinical trials show that infusing albumin solutions to maintain a near-normal plasma albumin concentration in patients with severe sepsis does not confer any therapeutic advantage (28).

Interstitial pressure (P_i) is the second absorptive Starling pressure. Once believed to be close to or slightly above atmospheric pressure, it is now known to be sub-atmospheric in most tissues of vertebrates where it has been investigated (29, 30). In human subjects, P_i is also slightly sub-atmospheric in subcutaneous tissues at heart level (31, 32). Noddeland (31) examined the effects of posture in 10 human subjects and reported a mean value of −1.4 mmHg at approximately heart level and a mean value of −0.4 mmHg at ankle level in standing subjects. The small difference between these mean values were not significant since the range of values was similar (−0.5 to +1.5 mmHg and −0.5 to +4.5 mmHg). There is evidence that P_i is more negative in the lungs (33). Acute inflammatory response arising within a tissue can drop the interstitial pressure even more negative, increasing the transendothelial filtration rate. Accumulation of tissue fluid eventually makes the interstitial pressure increasingly positive as lymphatic flow capacity is exceeded.

Transendothelial resistance to solvent flow (R_{te}) is not of itself a force, it nonetheless describes a characteristic of the microvasculature that explains physiological adjustments and is potentially amenable to therapeutic intervention (10).

Pore theory has been developed into a powerful mathematical model for describing microvascular fluid and solute exchange. The **small pores** are now generally believed to be the spaces between the fibrous molecules of the endothelial glycocalyx overlying the intercellular clefts of continuous endothelia or the fenestrae of fenestrated endothelia (34–36). The numbers of small pores engaged in the filtration process depend upon the number of breaks in the tight junctions which seal the intercellular clefts of continuous endothelia, and the numbers

of fenestrae in fenestrated endothelia. The **large pores** are believed to be either rare transendothelial or intercellular channels or possibly transcytotic vesicles (37). An important requirement for the maintenance of the permeability barrier is an uninterrupted supply of sphingosine-1-phosphate which is synthesized in healthy erythrocytes and bound to plasma albumin for transport to the endothelium (38). This important role of albumin in maintaining the capillary barrier requires quite a small concentration of endogenous albumin, and does not justify the administration of pharmaceutical albumin solutions to treat "leaky capillaries." The older notion that larger molecules should more successfully block large pores is erroneous.

THE HOCKEY STICK OR *J* CURVE RELATING STEADY STATE VALUES OF FILTRATION TO MICROVASCULAR PRESSURE

Starling believed that microvessels were impermeable to plasma proteins and that the concentrations of proteins in the interstitial fluids were very low. On this basis, he proposed that fluid movements between the plasma and the tissues should be self-limiting (4). For example, raised hydrostatic pressure in capillaries which drives fluid filtration from plasma to tissues concentrates the proteins of the plasma raising its colloid osmotic pressure which opposes filtration until it brings filtration to a halt. He saw this as a rapid means of regulating plasma volume.

Between the 1920s and late 1940s, evidence accumulated to show that proteins passed though capillary walls and were slowly circulating through nearly all the tissues of the body, being returned to the circulation by lymphatics. Apart from the liver, spleen and bone marrow, the permeability of microvessels in most other tissues to plasma proteins is low. It was appreciated that the protein permeability of microvessels meant that the effective colloid osmotic pressure opposing fluid filtration from plasma to tissue was reduced by a factor, the membrane reflection coefficient, σ. For capillaries and venules in most tissues, σ to macromolecules was 0.9 or more, so the effect was relatively small.

If microvascular walls are finitely permeable to proteins, the concentration difference across them, responsible for the colloid osmotic pressure difference, which Starling believed balanced the hydrostatic pressure difference, could not be maintained for more than a fraction of a second. There could be no "Starling equilibrium" because, in the absence of filtration, the colloid osmotic pressure difference would be dissipated by diffusion of protein from plasma to interstitial fluid. It was recognized that the protein concentration differences could be maintained by a low level of filtration since water and small solutes were carried into the interstitial fluid very much faster than large protein molecules. The resulting protein concentration in the ultrafiltrate would be considerably less than that in the plasma. The higher the filtration rate, the lower the concentration of protein in the ultrafiltrate. Consequently, the colloid osmotic pressure difference between plasma and interstitial fluid could be maintained constant by the greater trans-capillary flow rates of the fluid than of protein. While there would be no equilibrium, there could be a steady state difference.

This concept was developed quantitatively in a review of fluid exchange through microvascular walls (39). The steady state values of the colloid osmotic pressure difference depend on the hydrostatic pressures difference driving filtration, the permeability coefficients of the vessel walls and the plasma concentration of proteins. When evaluated for fluid exchange in tissues where permeability coefficients of the microvessels were known, the relation between hydrostatic pressure difference and filtration rate appeared as the "hockey stick" or "*J*" curve. The sharp change (inflection) from low slope to steep slope in most tissues of the systemic circulation occurs just below the colloid osmotic pressure of the plasma. Michel showed that some observations, previously believed to be inconsistent with the Starling Principle, could be accounted for by this steady state curve. The steady state relationship between hydrostatic pressure and filtration rate was later confirmed in experiments on single perfused microvessels where nearly all the variables could be estimated or controlled, for example (40).

The curve in **Figure 1** shows the filtration rates, which will maintain constant values of the colloid osmotic pressure difference across the walls of exchange vessels in a tissue at different microvascular hydrostatic pressures. If the microvascular hydrostatic pressures increase or decrease, transient filtration or fluid uptake will change the effective osmotic pressure differences across the microvascular walls to bring the filtration or reabsorption rates to the level consistent with the new hydrostatic pressure. Often a rise in microvascular hydrostatic pressure in one tissue are offset by simultaneous falls in pressure in another so that protein concentration in the circulating plasma is changed only slightly. If the change in pressure is large and persistent, however, the protein concentration of the plasma circulating through all tissues is changed. In this case, the curve and most conspicuously its inflection point is shifted along the pressure axis. Raised filtration rates in tissues below the heart during lengthy periods of standing concentrate the plasma proteins, raising plasma colloid osmotic pressure and shifting the curve with its inflection region to the right. Prolonged dilution of the plasma, as in auto-transfusion following hemorrhage, or infusion of crystalloid solutions, lower the plasma colloid osmotic pressure and the curve shifts to the left (see **Figure 2**).

The *J* Curve as a Clinical Concept

Woodcock proposed a simple paradigm for prescribers of fluid therapy inspired by the physiology described above. He called the inflected relationship between the net microvascular pressure and the whole-body transendothelial filtration rate the *J* curve. In this paradigm we expect the infusion of an intravenous fluid to increase plasma volume, and venous and capillary pressures, resulting in increased transendothelial solvent filtration rate. Of course, in the living animal, there are also endocrine responses to protect homeostasis, that include natriuretic peptide secretion and the renin-angiotensin-aldosterone pathway. If we infuse a

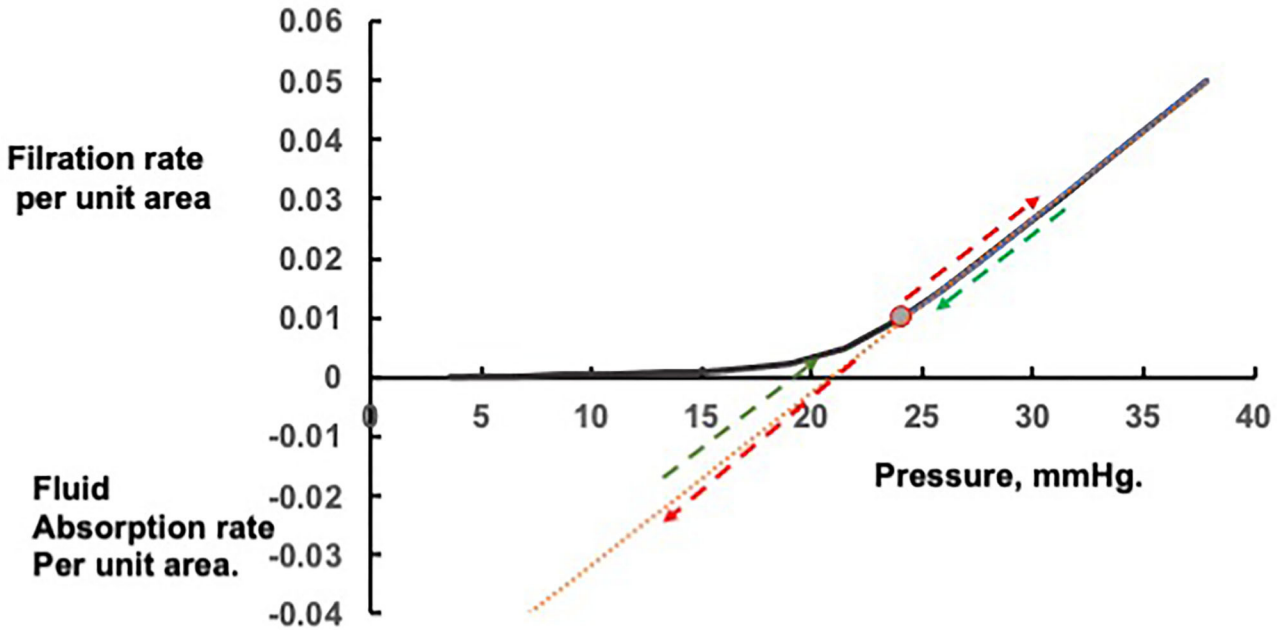

FIGURE 1 | Steady state and transient changes in fluid exchange with changes in microvascular pressure. Rapid changes in fluid filtration and absorption with step changes in pressure from the steady state are linear and indicated by the red arrows; rapid return to the original steady state pressure by the green arrows.

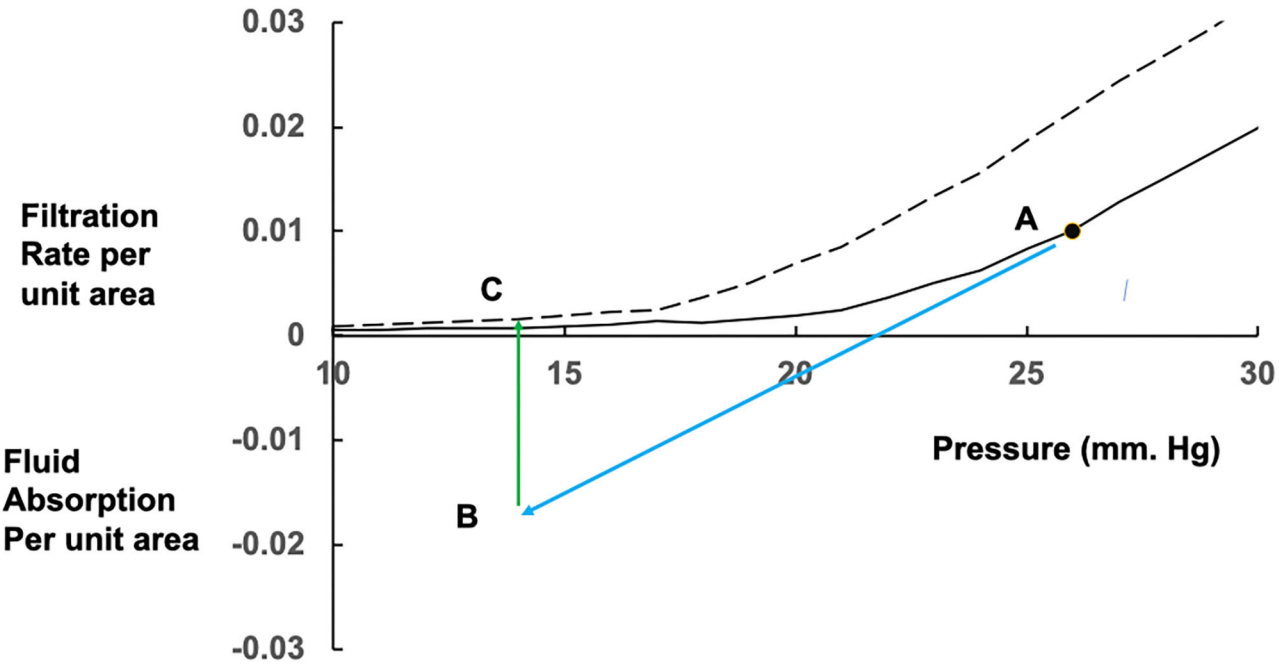

FIGURE 2 | Effects of prolonged fluid absorption on steady state relations between fluid exchange and microvascular pressure. From a position shown as point A on the initial steady state (solid) curve, a fall in mean microvascular pressure leads to a reversal of fluid exchange to fluid absorption (blue arrow) occurring at point B. If the fall in pressure is prolonged, fluid uptake dilutes the plasma protein concentration. Along with changes in the interstitial fluid, the colloid osmotic pressure difference falls, absorption rate falls and eventually reverses to a low level of filtration at point C on the new steady state curve (dashed), which has shifted to the left with the fall in plasma colloid osmotic pressure.

solution with no colloid osmotic pressure there is protein dilution and the colloid osmotic pressure of plasma falls, further favoring filtration. If we infuse a hyperoncotic solution of albumin (e.g., 20–25%) the colloid osmotic pressure of plasma (an absorptive force) increases, opposing filtration and shifting the curve to the right.

The *J* curve offers an explanation for the reported phenomenon of context sensitivity. In the face of falling capillary pressure, the transendothelial solvent filtration rate approaches zero, and may reverse to fluid absorption. The astute clinician notices that the colloid osmotic pressure of any resuscitation fluid he administers to a hypovolaemic patient (pressure <18 mmHg in **Figure 2**, below the *J* point) is of little importance while fluid is no longer leaving the circulation. We now have our explanation for the observed fact that the effective volume of resuscitation with a crystalloid solution is only a little greater than the effective volume of resuscitation with an iso-osmotic colloid solution.

THE EXTRAVASCULAR CIRCULATION OF EXTRACELLULAR FLUID

Spreading the message about this new physiology takes time. In 2010 Levick and Michel made the following plea (41).

> *Although doggedly persistent in textbooks and teaching, the traditional view of filtration–reabsorption balance has little justification in the microcirculation of most tissues. Tissue fluid balance thus depends critically on lymphatic function in most tissues. In making these forceful statements, we are mindful of William Harvey's remark in his classic, De Motu Cordis (1628): 'I tremble lest I have mankind for my enemies, so much has wont and custom become second nature. Doctrine once sown strikes deep its root, and respect for antiquity influences all men'.*

This emotive *cri de couer* led Woodcock and Woodcock to consider consequences and implications for the physiologically rational prescription of intravenous fluids (42), bringing the glycocalyx model into the core knowledge base for clinicians (43). Nonetheless, there remain modern day enemies of this challenge to "wont and custom" (44). There had been previous clues that the Starling principle as taught in the twentieth century could not explain fluid physiology as experienced by clinicians. Cope and Litwin had reported in 1962 that, contrary to Starling principle expectations, plasma volume refill after acute hemorrhage in a canine experiment was attributable to a rise in thoracic duct lymph flow. Lymph flow returned about twice the amount of protein that had been lost by hemorrhage. They called this phenomenon "the essentiality of the lymphatic system to the recovery from shock" (45).

In human volunteer studies published in 1966 F.D. Moore (46, 47) observed that normal transcapillary refill after hemorrhage in man does not involve any significant period of hypoalbuminaemia, which would occur if refilling was solely due to capillary reabsorption of solvent and small solutes. After a 12% reduction in blood volume, the plasma refill rate in these adult male volunteers was about 1 ml per minute. Moore was concerned that crystalloid resuscitation might cause a washout of plasma proteins to the tissues, but in a volume kinetic experiment on the same subjects he found that, while two thirds of infused isotonic salt solution was leaving the circulation, approximately 15–17 g protein (mostly albumin) was entering the plasma. The saline infusion, rather than producing a washout of plasma protein to the interstitium, appeared to restore interstitial fluid volume sufficiently to support protein flow to the plasma. He also presciently warned that "much larger saline infusions, by producing a more drastic protein dilution, might mask this effect completely, leading to the erroneous interpretation of washout." From the volume kinetics of this crystalloid infusion Moore even determined that the net vector of fluid exchange from plasma to interstitial fluid, and from interstitial fluid to plasma, is about 5 ml per minute. Though he did not realize it, Moore was measuring the extravascular circulatory rate of extracellular fluid. We now know that, in healthy steady state conditions, around 300 ml per hour of solvent and electrolytes leaves the plasma, mostly by transendothelial solvent filtration (48–50), around 8 L per day being absorbed into the lymphatic system (as predicted by William Hunter) and then carried by afferent lymphatic vessels to lymph nodes, where approximately half is absorbed to the blood stream through the diaphragm-fenestrated high endothelia of the lymph node capillaries and venules. The remainder is propelled as efferent lymph to the thoracic duct, and thereby returned to the blood stream in the great veins. Similar studies on species encountered in veterinary practice would be needed to estimate the magnitude of extracellular fluid circulation in them.

The preceding considerations apply to most tissues, most of the time. There are tissues in which there is sustained absorption of fluid from tissue into the blood stream. This is possible because in these tissues, proteins of the interstitial fluid are continually diluted by sources other than filtration from local microvessels. Examples are epithelial secretions into the interstitial fluid of protein free fluid, as in post-glomerular vessels of the kidneys, or the flow of lymph through the interstitium of the lymph nodes. The intestinal microcirculation is able to sustain absorption of ingested fluid when it is available, and to sustain filtration during fasting. Capillaries in such tissues often have circular windows of fused luminal and abluminal endothelial cell membrane; the diaphragm fenestrated capillaries.

Woodcock commends to clinicians a kinetic perspective on the distribution of extracellular fluid between the intravascular and extravascular compartments, revealing ways in which plasma volume can be manipulated therapeutically (10). In **Figure 3**, the free-flowing plasma is shown in pink, while the intravascular gel phase (the endothelial surface layer), the volume of circulating blood cells and the extravascular gel-phase interstitial fluid is shown in yellow. The central volume of distribution V_c of an isoncotic intravenous colloid infusion is largely restricted to the free flowing plasma. The central volume of distribution V_c of an isotonic intravenous crystalloid infusion includes the whole of the intravascular space. The tissue volume of distribution Vt of a crystalloid infusion is limited to the expansile tissues, and is much less than the total extracellular fluid (ECF) volume.

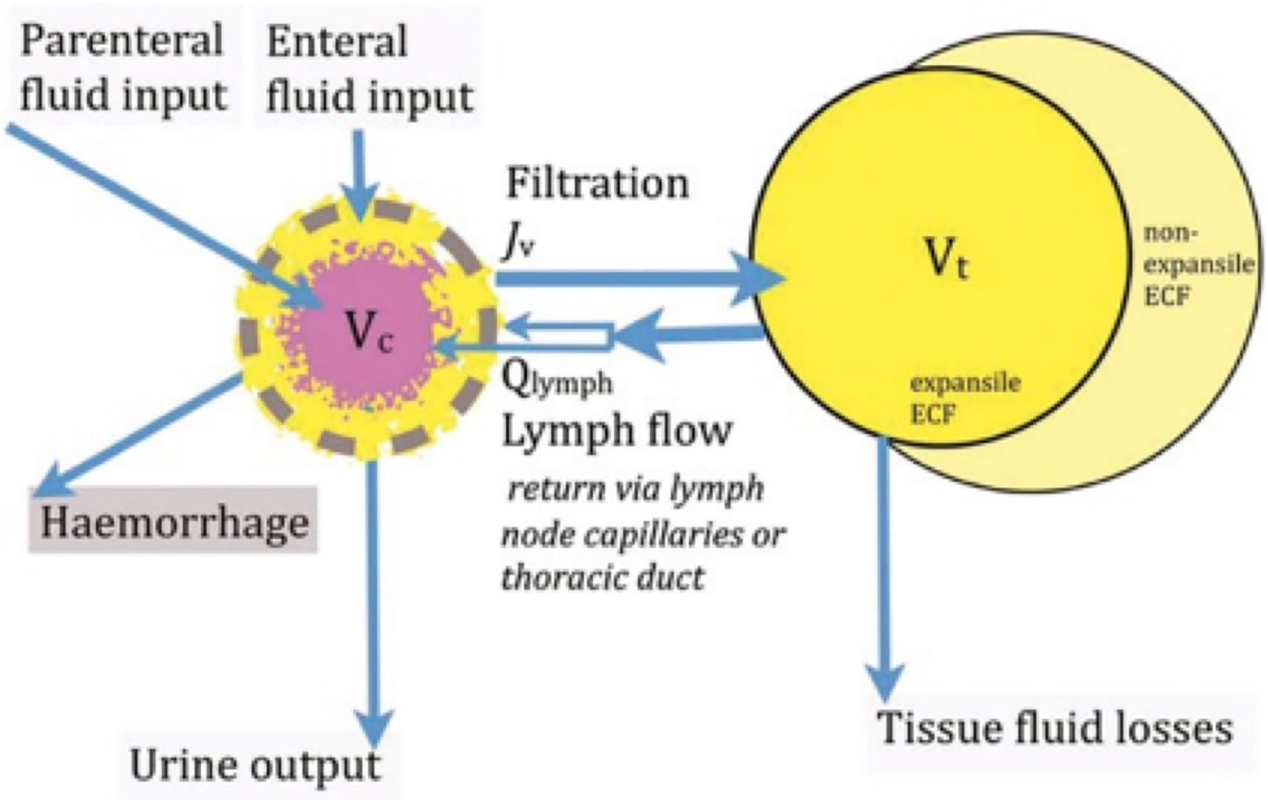

FIGURE 3 | The central volume of distribution Vc of an isosmotic colloid approximates to the free flowing plasma, while the Vc of an isotonic intravenous crystalloid infusion includes the whole of the intravascular space. The tissue volume of distribution Vt of a crystalloid infusion is limited to the expansile tissues, and is much less than the total extracellular fluid (ECF) volume.

PLASMA VOLUME

As illustrated in **Figure 3**, plasma volume accumulates by absorption of ingested fluids, the absorption of solvent and small solutes from lymph by lymph node microvessels, and the delivery of efferent lymph to the central veins (51, 52). Our patients face the additional challenge of intravenous fluid infusions. Plasma volume is reduced by urine output and by transendothelial solvent filtration. Surgery, trauma and burns add pathological blood and tissue fluid losses to our considerations. An important contributor to healthy plasma volume homeostasis is the tonic regulation of capillary permeability to albumin. Arteriolar constriction with an infusion of norepinephrine supports plasma volume by reducing capillary pressure so diminishing fluid filtration. Notice that norepinephrine also increases the stressed blood volume, or the effective arterial blood volume if you prefer that concept. In a patient who was not hypovolaemic, norepinephrine infusion can increase urine output. Norepinephrine infusions are increasingly being used in critical care practice to counteract the reduced arterial diastolic pressure and increased capillary pressure associated with deep general anesthesia, epidural anesthesia and systemic inflammatory response. It is obviously vital to avoid higher doses which can lead to tissue ischaemia.

In 1832 Scottish physician Thomas Aitchison Latta pioneered the use of intravenous saline solution for patients dehydrated by cholera. Today we understand that these patients became ill when plasma volume was so reduced that the available venous excess was too small to permit the diastolic right ventricle to fill to normal stroke volume (53, 54). By infusing an isotonic salt solution Latta was resuscitating the intravascular volume, restoring the venous excess volume and increasing the capillary and venular hydrostatic pressures. With reference to the *J* curve, notice that at very low capillary pressure transendothelial solvent filtration and glomerular filtration rates are minimal so that net accumulation of volume is maximized, increasing capillary and venular pressures. Using a colloid resuscitation fluid would be only slightly more efficient than the crystalloid, because preserving plasma colloid osmotic pressure during hypovolaemia has only minimal effect on the transendothelial filtration rate. Because of their lower density and viscosity, crystalloid solutions can be infused more rapidly and will more quickly restore the trans-endothelial and glomerular filtration rates, with greater urine output. The oft-stated logic that "colloids stay in the circulation longer" is misleading; what we need to focus on is the transendothelial and glomerular filtration rate consequences of infusing any intravenous fluid.

There are clinicians whose practice is to infuse fluids to normovolaemic patients with the intention of creating a hypervolaemic hyperdynamic circulatory state, to the point at which further volume expansion is no longer associated with increased stroke volume. For no obvious reason this is often called volume optimisation. Oxygen delivery is often not increased because of dilutional anemia and reduced oxygen content. Referring to the *J* curve, the capillary pressure is rising from normal toward capillary hypertension with increased transendothelial solvent filtration. If this volume expansion

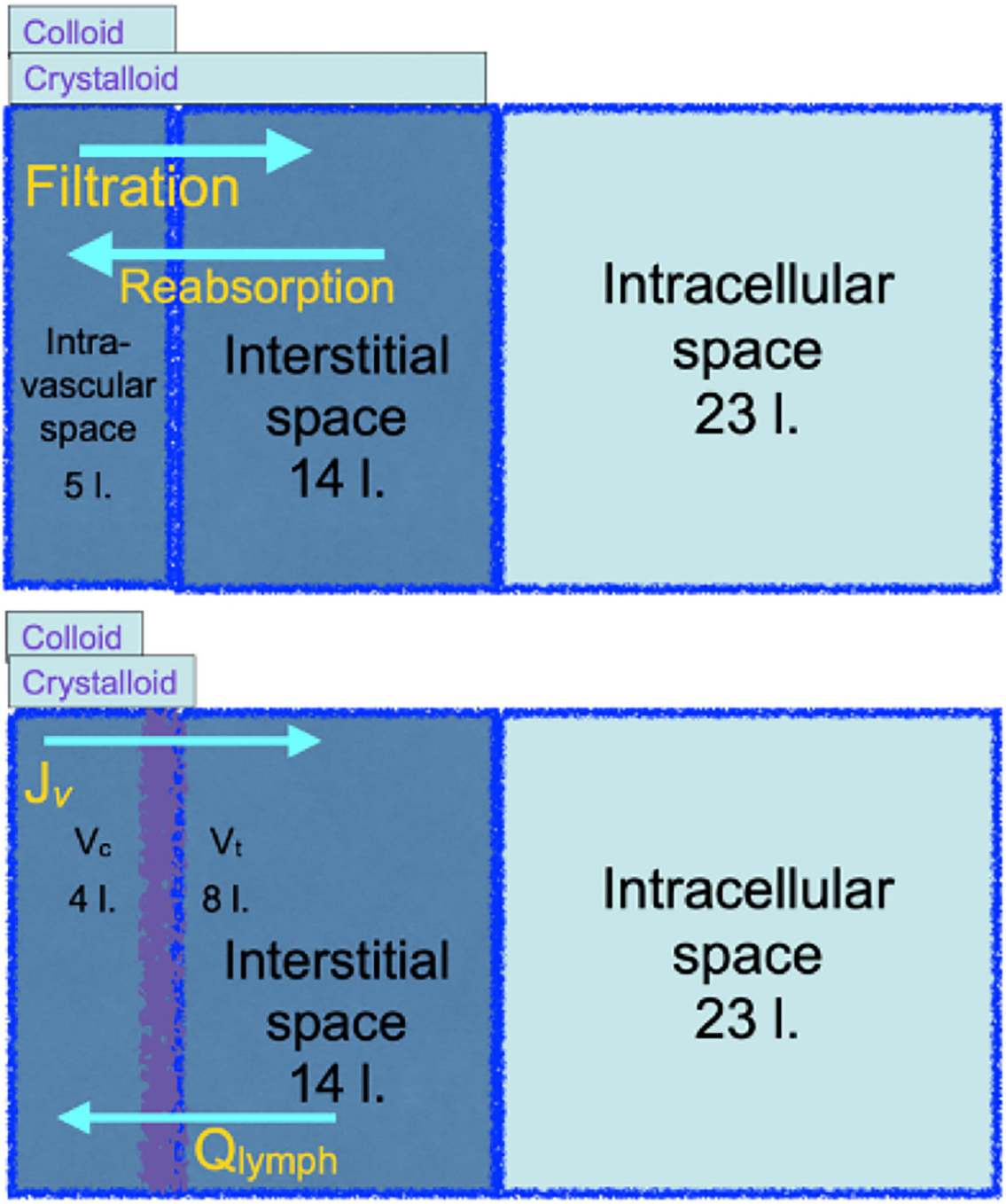

FIGURE 4 | The top cartoon is a familiar illustration of the distribution of body water in original Starling physiology theory that implies that crystalloid solutions will be inefficient for resuscitation from a reduced plasma volume. The bottom cartoon, grounded in revised Starling physiology, explains the observed relative efficiencies of either colloid or crystalloid resuscitation.

TABLE 1 | A comparison of clinical expectations based upon the Original or Extended Starling principle paradigms.

Original starling principle paradigm	Extended starling principle or glycocalyx model paradigm
Intravascular volume consists of plasma and cellular elements.	Intravascular volume consists of glycocalyx volume, plasma volume, and cellular elements.
Capillaries separate plasma with high protein concentration from interstitial fluid (ISF) with low protein concentration.	Sinusoidal tissues (marrow, spleen, and liver) have *discontinuous capillaries* and their interstitial fluid (ISF) is essentially part of the plasma volume. *Open fenestrated capillaries* produce the renal glomerular filtrate. *Diaphragm fenestrated capillaries* in tissues with an independent supply of fluid to the interstitium can sustain absorption of ISF to plasma. *Continuous capillaries* exhibit 'no absorption'. The endothelial glycocalyx is semi-permeable to proteins and their concentration in the microdomain below the glycocalyx varies with transendothelial solvent filtration (*Jv*).
The important Starling forces are the transendothelial pressure difference and the plasma–interstitial colloid osmotic pressure difference operating across a porous endothelial barrier.	The important Starling forces are the transendothelial pressure difference and the plasma – subglycocalyx colloid osmotic pressure difference operating across the continuous glycocalyx.
Fluid is filtered from the arterial end of capillaries and absorbed from the venular end, while a small proportion returns to the circulation as lymph.	Transendothelial solvent filtration (*Jv*) is much less than predicted by Starling's principle, and the major route for return to the circulation is as lymph.
Raising plasma colloid osmotic pressure enhances absorption and shifts fluid from ISF to plasma.	Raising plasma colloid osmotic pressure reduces *Jv* but does not cause sustained absorption of ISF. Auto transfusion after abrupt disequilibrium is a transient and limited phenomenon.
At subnormal capillary pressure, net absorption increases plasma volume.	At subnormal capillary pressure, *Jv* approaches zero. Auto transfusion after abrupt disequilibrium is a transient phenomenon, and limited to about 500 ml.
At supranormal capillary pressure, net filtration increases ISF volume.	At supranormal capillary pressure, when the colloid osmotic pressure difference is maximal, *Jv* is proportional to the transendothelial pressure difference.
Infused colloid solution is distributed through the plasma volume, and infused isotonic salt solution through the extracellular volume.	Infused colloid solution is initially distributed through the plasma volume, and infused isotonic salt solution through the intravascular volume. At supranormal capillary pressure, infusion of colloid solution preserves plasma colloid osmotic pressure, raises capillary pressure, and increases *Jv*. At supranormal capillary pressure, infusion of isotonic salt solution also raises capillary pressure, but it lowers colloid osmotic pressure and so increases *Jv* more than the same colloid solution volume. At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of isotonic salt solution increases intravascular volume, but *Jv* remains close to zero in both cases.

is induced with crystalloids, colloid osmotic pressure of plasma is reduced as the capillary hydrostatic pressure rises. Compensation by filtration and return to normovolaemia is therefore rapid. Colloid solutions preserve or even increase the colloid osmotic pressure of plasma, slowing the compensation rate and prolonging the hypervolaemic state. There is no clinical evidence that this practice is of greater benefit to patients than other perioperative fluid management strategies (54).

In modern perioperative care the available evidence suggests the optimal goal for fluid balance is a modest positive balance which guards against intravascular hypovolaemia, with minimal harm from oedema or heart failure. There is no evidence that the use of synthetic colloids or albumin is necessary to achieve optimal patient outcome (54).

A NEW PHYSIOLOGICALLY-BASED PARADIGM FOR RATIONAL FLUID THERAPY PRESCRIPTION

In 1985 Twigley and Hillman announced 'the end of the crystalloid era' (55). Using a simplified diagram of plasma, interstitial and intracellular fluid compartments, and their anatomic volumes, they argued that colloids could be used to selectively maintain the plasma volume. Plasma volume being about 20% of the extracellular fluid (ECF), it was presumed that the volume equivalence for resuscitation from intravascular hypovolaemia would be of the order of 100 ml isotonic salt solution to 25 ml colloid. Moreover, it was presumed from Starling's principle that transfusion of hyperoncotic colloid solutions would sustain absorption of fluid from the interstitial fluid to the intravascular volume. This simple concept of colloid for plasma volume and isotonic salt solution for extracellular fluid replacement has been continued and developed. For adult human body water, see the top diagram, **Figure 4**.

Large randomized clinical trials reported in the twenty first century to date unanimously reject the concept of crystalloid inefficiency as a resuscitator from reduced plasma volume. The bottom diagram, **Figure 4**, updates the familiar body water diagram, with the expected central volumes of distribution of a colloid or a crystalloid infusion. The SAFE study of 2004 (56) looked at critically ill patients over the first 4 days of fluid resuscitation. 100 ml isotonic salt solution was as effective as 62–76 ml human albumin solution in the SAFE study, or 63–69 ml hyperoncotic plasma substitute in VISEP (57). The FIRST study enrolled blunt trauma patients during the first day

of resuscitation, in whom 100 ml isotonic salt solution was as effective as 97 ml isosmotic plasma substitute, while in gunshot or stabbing victims, 100 ml was as effective as 67 ml (58). After Woodcock's paradigm was published in 2012, three further trials were published. All reported the volume equivalence for resuscitation of hydroxyethyl starch to 100 ml isotonic salt solution. The CHRYSTMAS study averaged 80 ml (59), the CHEST study 85 ml (60), and the 6S trial reported the median cumulative volume of fluid received was 3,000 ml in both groups (61). The FLASH randomized controlled trial gave resuscitative equivalents of 100 ml saline to be 83 ml hydroxyethyl starch (62). It is often noted that the colloid treated patients receive more blood transfusions, which the Woodcock paradigm attributes to greater haematocrit reduction by colloids. In the ALBIOS study, administration of human albumin solution to keep the plasma albumin concentration above 30 g/ l did not reduce the intravenous fluid volume administered and had no effect on patient outcome (28).

The new formulation of the century old Starling principle inspired a new clinical paradigm for fluid therapy (**Table 1**) that draws on the extended Starling principle and an appreciation of all the Starling forces, and understands the many limitations of biophysical colloid osmotic pressure therapy. It reminds us of the importance of protecting and even enhancing lymphatic pump efficiency to boost the plasma volume. It suggests ways in which alpha-adrenergic agonists, and perhaps other vasoactive agents, can be prescribed in doses that optimize capillary and venular pressures for circulatory blood flow and trans-endothelial solvent filtration (63). New avenues of research are needed (64).

AUTHOR CONTRIBUTIONS

TW was invited to contribute this narrative review to be one in a themed series and is responsible for interpretation of the consequences and implications of Starling physiology for fluid therapy, created **Figures 3** and **4**. CM developed the explanation of Starling physiology as presented here and created **Figures 1** and **2**. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Effects of Resuscitative Fluid Therapy on the Endothelial Surface Layer

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The goal of resuscitative fluid therapy is to rapidly expand circulating blood volume in order to restore tissue perfusion. Although this therapy often serves to improve macrohemodynamic parameters, it can be associated with adverse effects on the microcirculation and endothelium. The endothelial surface layer (ESL) provides a protective barrier over the endothelium and is important for regulating transvascular fluid movement, vasomotor tone, coagulation, and inflammation. Shedding or thinning of the ESL can promote interstitial edema and inflammation and may cause microcirculatory dysfunction. The pathophysiologic perturbations of critical illness and rapid, large-volume fluid therapy both cause shedding or thinning of the ESL. Research suggests that restricting the volume of crystalloid, or "clear" fluid, may preserve some ESL integrity and improve outcome based on animal experimental models and preliminary clinical trials in people. This narrative review critically evaluates the evidence for the detrimental effects of resuscitative fluid therapy on the ESL and provides suggestions for future research directions in this field.

Keywords: endothelium, glycocalyx, shock, fluid therapy, crystalloid, colloid, endothelial surface layer

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INTRODUCTION

The importance of microcirculatory function and health of the endothelium has become a large area of interest for criticalists in the last two decades. Over this time, fluid resuscitation strategies have experienced a shift in perspective. Aggressive "clear" fluid resuscitation was once considered vital for stabilization of macrohemodynamic variables. However, in certain patient cohorts this approach has now been shown to either not improve outcome or worsen outcome (1–4). Though fast administration of fluid often serves to normalize the commonly measured clinical parameters during shock, microcirculation may not necessarily benefit from this therapy. There is growing evidence that fluid resuscitation may actually harm the endothelium by modifying, or shedding, the endothelial surface layer (ESL).

The ESL includes a structural scaffold, the endothelial glycocalyx (EG), and associated molecules suspended within a plasma layer. We use the term *EG* when referring to specific components of the structure, or biomarkers of these components, whereas ESL is used when referring to the layer as a whole. In regards to shedding of the ESL, the term *ESL* will be used when the evidence supports loss of the whole layer and the term *EG* used when the evidence only supports that isolated components have been shed. Use of the term *glycocalyx* refers to any type of cell surface glycocalyx and is not restricted to the endothelium, such as during discussion of glycocalyx shedding biomarkers.

Resuscitative fluid therapy includes a range of fluid choices, including isotonic crystalloid fluid, synthetic colloid fluid, and hyperosmolar crystalloid fluid, with the former being the most common type of fluid used (5). In general, due to the pharmacodynamic properties of these fluids in either healthy subjects or shock models (6–9), the volume of fluid is "large" for isotonic crystalloid (at least a quarter to half of estimated blood volume), "moderate" for synthetic colloid (an eighth to quarter of estimated blood volume), and "small" for hyperosmolar crystalloids. All three types of fluid resuscitation will be covered in this review with a particular focus on isotonic "large-volume" crystalloid fluid therapy due to the evidence for its effects on the ESL. A summary of the evidence reviewed in this article is provided in **Box 1**.

BOX 1 | Summary of the evidence for effects of "clear" fluid therapy on endothelial surface layer (ESL) shedding or modification.

Proposed mechanisms of ESL shedding
- Dilution of plasma proteins
- Release of natriuretic peptides
- Inflammatory cytokine release (certain fluid types)

Possible downstream effects
- Exacerbation of inflammation
- Microcirculatory dysfunction
- Increased vascular permeability
- Increased interstitial edema
- Prothrombotic conditions

Proposed strategies that may mitigate ESL shedding*
- Reduction in dose of clear fluids
- Slowing down administration of resuscitative fluids
- "Earlier" vasopressor therapy for vasodilatory shock
- Adjunctive protein administration (such as plasma)

*These proposed strategies are not based on evidence from clinical veterinary research and require further investigation. These guidelines are opinion of the authors only, after considering the breadth of evidence available. It is currently unknown if "glycoprotective" strategies benefit patients. Therapy should always be tailored to individual patient needs, with prioritization of reestablishing adequate perfusion and a thorough cost to benefit analysis.

STRUCTURE AND FUNCTION OF THE ENDOTHELIAL SURFACE LAYER

Basic Structure and Function

Most cells in the body are covered in a protective layer of carbohydrate scaffold, which houses many different molecules that serve a variety of functions. This surface layer is called a glycocalyx. The general structure of the glycocalyx has similarities between cell types, with only small variations in individual proteins or carbohydrate molecules. The EG coats the luminal surface of the endothelium and is a vital structure for cell signaling and transvascular permeability. It is composed of proteoglycans, glycosaminoglycans (GAGs), and glycoproteins (**Figure 1**). Together with mobile or soluble components, such as albumin, this compromises the ESL. Proteoglycans are large molecules that have a cytoplasmic, transcellular, and extracellular domain (syndecan) or are attached by a glycosylphosphatidylinositol anchor (glypican-1) (**Figure 1**) (10–12). Their extracellular component, or ectodomain, is covered by GAG side-chains and performs important roles that assist with cell to cell, or cell to matrix, interactions (13). These structures provide a structural scaffold for the ESL, in which many other molecules are housed. The sulfated GAGs attached to proteoglycans include heparan, chondroitin, and dermatan sulfate. Heparan sulfate is the most abundant GAG on syndecans and glypican-1, which is why proteoglycans are often referred to as heparan sulfate proteoglycans. An additional GAG, hyaluronan, is not typically associated with a proteoglycan; instead, it is attached to the endothelium via receptors such as CD44 or other GAG molecules (**Figure 1**) (14, 15). Hyaluronan is a long GAG of varying lengths that weaves its way through the tall "forest" of proteoglycans, with their sulfated GAG "branches". These GAG chains contribute to the barrier function of the ESL of excluding large molecules (16). Glycoproteins reside on the luminal surface of the endothelium, hidden within the ESL, and include adhesion molecules such as integrins and selectins (17). Glycoproteins play an important role in leucocyte trafficking during states of inflammation (18); many of their functions are only initiated once the ESL has been shed or thinned. Finally, mobile components residing within the forest of the ESL include proteins, such as albumin, and anticoagulants, such as antithrombin and tissue factor pathway inhibitor (15, 19). The presence of plasma proteins are likely important for maintaining the normal structure and permeability of the ESL, as well as providing an anticoagulated surface at the blood interface.

The EG serves a range of functions, many of which are still being characterized. These functions include maintenance of a surface barrier that buffers circulating leucocytes, inhibits coagulation, regulates fluid flux, and communicates changes in vascular wall shear forces. The sulfated GAGs on the surface of the endothelium generate and maintain a net negative charge, which repels similarly charged cells from the endothelial surface (20). Although albumin has an overall negative charge, it is likely that the positively charged groups within the molecular structure are what allow for incorporation of albumin into the ESL (21). Maintenance of this negative charge is important for endothelial integrity; loss of negative charge on the luminal surface of the endothelium leads to extravasation of albumin (22–24). In addition to the importance of electrostatic charge, the ESL provides a barrier to fluid filtration, thus creating a protein-poor sub-glycocalyx layer and maintaining a colloid osmotic pressure (COP) gradient favoring fluid retention within the vasculature (20).

The traditional Starling hypothesis describes a relationship between the intravascular and the interstitial colloid osmotic pressure and implies the importance of this relationship in determining net transvascular fluid filtration. Many studies in the last four decades, however, have built a body of evidence stating that it is mainly the low COP in the sub-glycocalyx area that creates the pressure gradient opposing capillary hydrostatic pressure (25, 26). The theory is that the

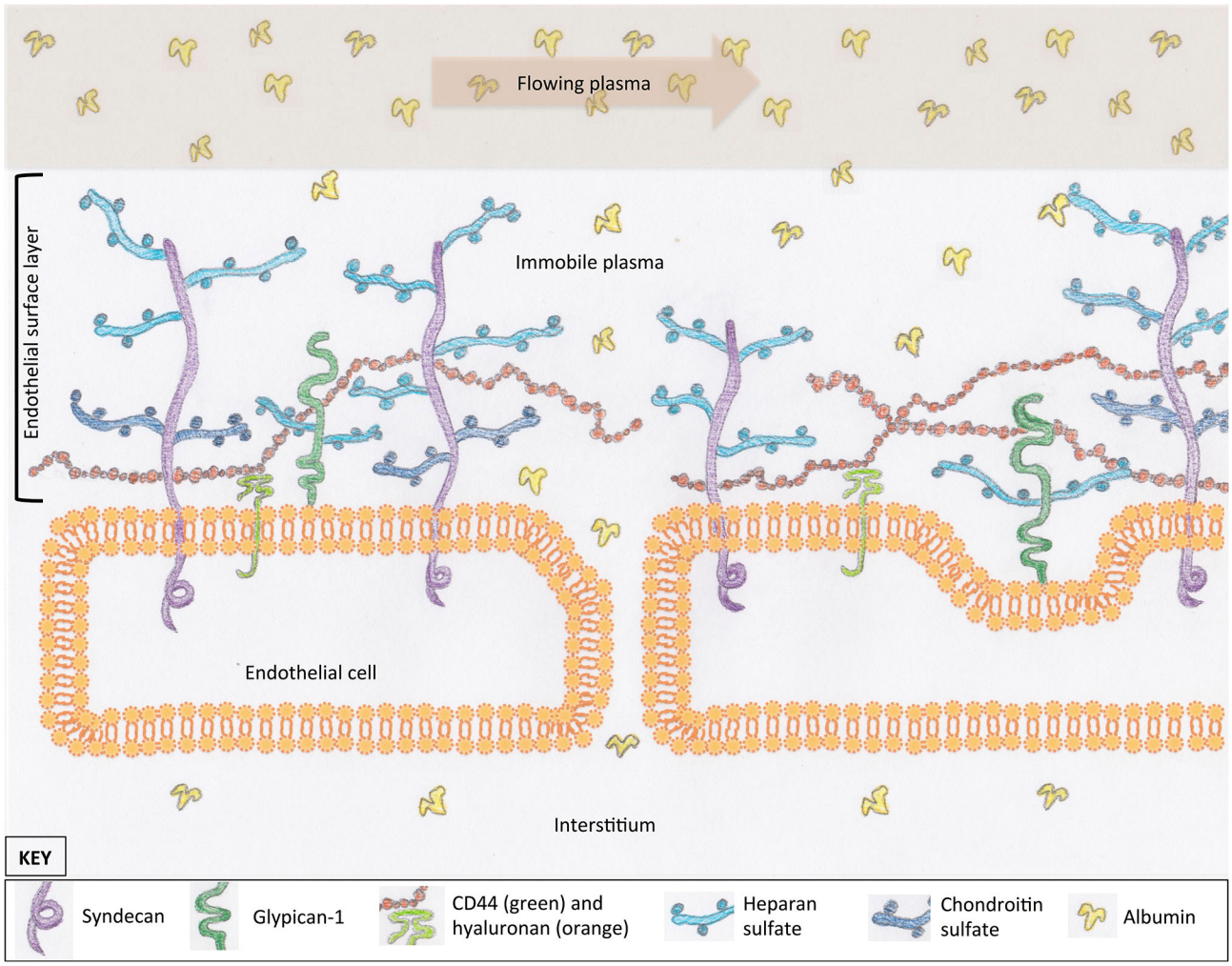

FIGURE 1 | The scaffold of the endothelial glycocalyx, within the endothelial surface layer, is provided by proteoglycans, syndecan (four subtypes), and glypican-1. Glycosaminoglycans are attached to proteoglycans (e.g., heparan sulfate) or the endothelial surface (hyaluronan). Molecules suspended in the plasma of the endothelial surface layer include proteins such as albumin. These proteins create a protein-poor sub-glycocalyx area that is important for transvascular colloid osmotic pressure balance. For simplicity, structures within the interendothelial cleft are not represented.

sub-glycocalyx fluid space, within the inter-endothelial cleft, has a very low concentration of macromolecules. This is due to the high impermeability of the ESL to macromolecules and the rapid flow of water and solutes through the sub-glycocalyx space (27). In the steady state with an intact ESL, net filtration of fluid occurs across the blood vessel wall, with only a small limitation from intravascular COP. Increasing intravascular COP does not, and cannot, serve to reverse net fluid transudation nor does increasing interstitial COP lead to an increase in fluid transudation (28, 29). A large drop in hydrostatic pressure, such as that may occur during circulatory shock, may reverse transvascular fluid flow to a resorptive state; however, this effect is transient (29). These hypotheses explain why fluid would not be "drawn" out of the interstitium by increasing intravascular COP, such as the use of synthetic colloid fluids. Rather, they can reduce extravasation compared to crystalloid fluid. The COP of the intravascular space, and even of the sub-glycocalyx space, is microanatomically and physiologically distant from the interstitial COP. However, the fluid dynamics across the endothelium in disease states with a denuded ESL, removing the influence of the sub-glycocalyx layer, is yet to be fully characterized.

The EG also plays an important role to changing pressures and flow within the intravascular space. Proteoglycans, especially those with heparan sulfate chains, play an important role in responding to changes in vascular wall shear stress or changes in intravascular pressure (10, 30, 31). Detection of these mechanical forces leads to morphological changes in endothelial cells and release of nitric oxide (32–35). Shear stress can also lead to a change in location of proteoglycans or upregulation of their cell surface expression (36–38). It is possible that change in location or upregulation of these molecules during microcirculatory disturbances may also affect shedding of the extracellular

components. This becomes relevant when discussing biomarkers for EG shedding below.

Shedding

Shedding, or modification, of the ESL is a vital step after tissue injury in order to facilitate leucocyte and platelet adherence (39). Shedding reproduced in cell culture or *ex vivo* models leads to increased expression of adhesion molecules, increased leucocyte adhesion, and increased cytokine production (32, 40–43). This process is likely more complex *in vivo*, whereby certain disease states may have varying effects, from selective removal of glycocalyx components to complete denudation. Although ESL shedding is a necessary step in localized inflammation, it is becoming clearer that systemic-wide shedding is associated with severity of illness and poor outcome. There has also been a growing concern in recent years that interventions that promote ESL shedding may worsen clinical outcomes for critically ill patients. Given that ESL shedding is associated with exacerbating inflammation and increasing vascular permeability in laboratory models, there is theoretical plausibility that limiting ESL shedding may improve clinical outcome.

Shedding alters capillary perfusion, causing a decrease in functional capillary density (44), in addition to increased endothelial permeability (45). A decrease in functional capillary density means that some vessels within a given area do not have red blood cells traversing their course, consistent with microcirculatory dysfunction. This can create regions of tissue hypoxia. A clear association between ESL shedding and impairment of microcirculatory blood flow is yet to be demonstrated in either an *in vivo* animal model or clinical study (46). However, given that ESL shedding via artificial means can reduce capillary blood flow (44), it is mechanistically plausible that shedding of the ESL in critical illness plays a role in altered microcirculation. It has been well-demonstrated that heterogeneity of capillary blood flow can persist in critical illness despite normalization of macrohemodynamic variables, such as blood pressure and cardiac output (47–51). Further, persistence of altered microcirculatory flow in critically ill people is associated with severity of illness and poor outcome (47, 51–53). Consequently, it appears important to identify causes of microcirculatory dysfunction that occurs independent of circulatory shock. More evidence is required to determine a causal link between ESL shedding and microcirculatory dysfunction, and whether protection of the ESL can prevent the latter.

There may be downstream consequences to the release of EG components into circulation. Shed components can stimulate inflammation by acting as danger-associated molecular patterns or "alarmins." Soluble heparan sulfate molecules play a key role in modulating inflammation, including leukocyte activation, increasing production of cytokines, and endothelial activation (54, 55). Low molecular weight hyaluronan can also stimulate production of inflammatory mediators (56–59). In contrast, shed components such as syndecan-1 and−4 ectodomains can have indirect anti-inflammatory effects by facilitating neutrophil cytotoxicity (60, 61). The complexity of EG components acting as effector molecules in the systemic circulation may be analogous to the systemic inflammatory response, where some cytokine release is beneficial to the host response, whereas a "cytokine storm" creates pathological consequences.

It is unclear how long it takes for ESL recovery to occur. Most evidence is based on data from *in vitro* cell culture or *ex vivo* vascular models, which are unable to fully replicate *in vivo* conditions. That being said, individual components can be regenerated within 24 h (37, 62), but restoration of the structure itself can take up to 7 days (32, 63). During critical illness, inflammation likely continues the shedding process, delaying the repair. Further *in vivo* research is required using real-time videomicroscopy or similar means in order to characterize the temporal changes during ESL recovery.

Assessment of Shedding

Shedding of the ESL can be detected by a number of means. Laboratory studies utilize several methods, including measurement of circulating components of the EG (proteoglycan ectodomains and GAGs), detection of EG components on the surface of the endothelium, direct visualization of the ESL via tissue fixation and microscopy, and indirect visualization via real-time videomicroscopy. Clinical studies usually rely on measurement of circulating components of the EG, or EG biomarkers, in serum or plasma samples to assess systemic shedding. The most frequently reported EG biomarkers are syndecan-1, heparan sulfate, and hyaluronan. There are several limitations to relying on this kind of assessment of the ESL. Firstly, studies often only measure a single component of the EG at a single point in time. That particular component may have other sources of shedding. For example, syndecan-1 is not only present on the surface of the endothelium but also on epithelial cells and leucocytes (64–68). Also, highly relevant to intravenous fluid therapy, hyaluronan is abundant throughout the interstitium and can be "flushed" through the lymphatics back into systemic circulation (69–71). It is unclear in critical illness to what degree other sources of glycocalyx shedding contribute to serum or plasma concentrations. Further, tissue injury and inflammation during critical illness may upregulate cell surface expression of these biomarkers, especially the proteoglycans (38, 72–83). Therefore, an increase in circulating concentration may reflect an increase in cell turnover rather than primarily cell surface shedding. Several recent studies have demonstrated temporal differences in the shedding of several EG components in people presenting to an emergency department with sepsis, whereby hyaluronan increased early in treatment whereas sydnecan-1 increased later (84–86). This raises questions as to why some biomarkers increase earlier than others. It is possible that the temporal differences relate to either alternative sources of the biomarker or differences in upregulation.

Ideally, it would be best to visualize shedding of the EG *in vivo* rather than interpreting circulating biomarker concentrations. These techniques are mostly reserved for use in laboratory models rather than clinical use. Specialized tissue fixation techniques can be used to directly visualize the ESL via electron microscopy, often employed in non-survival rodent models (28, 87–91). Given the fragility of the ESL, it is best that the tissue is preserved via perfusion with fixative prior to death,

either perfusion of an isolated organ or the whole body. Tissue immersion techniques that avoid whole-body perfusion have also been recently described (92). Anecdotally, it is challenging to achieve quality images of intact ESL in tissue sections. Alternatively, components of the EG may be fluorescently labeled and visualized by confocal microscopy of cell culture or tissue models (93). Other laboratory techniques include dye exclusion with intravital microscopy to estimate ESL thickness (94–96). Finally, ESL thickness may be estimated in real-time by sidestream dark field microscopy in both large animal models and clinical research (46, 97–99). This technology approximates ESL thickness by measuring the perfused boundary region, which is the region within the blood vessel that is peripheral to the flow of red blood cells, or the immobile plasma layer. Although this technique shows promise for future use in veterinary clinical research (100), image acquisition can be technically difficult and image quality is currently limited for reliably estimating ESL thickness.

MECHANISMS OF SHEDDING RELEVANT TO FLUID THERAPY

Inflammation and Shock

In the patient requiring bolus fluid therapy, it is likely that alteration of the ESL has already occurred due to the effects of inflammatory mediators. For example, tumor necrosis factor-α, a potent pro-inflammatory cytokine, causes reduction in thickness of the ESL, shedding of syndecan-1,-4, and GAGs from the endothelium, as well as upregulation of glycocalyx components on the endothelial surface (76, 81, 90, 101). Matrix metalloproteinases, one of the main perpetrators for glycocalyx shedding, are released by activated leucoytes (17). Tissue injury, such as ischemia and reperfusion, and production of reactive oxygen species also cause EG shedding (43, 102–104). Activation of coagulation may also affect the EG, as both plasmin and thrombin can cleave syndecan ectodomains (74, 105). Relevant to sepsis, bacterial components such as lipopolysaccharide and chemotactic peptides also cause shedding of the EG (43, 77, 81, 106–108). Therefore, it is likely that partial or complete denudation of the ESL has already occurred before fluid therapy is administered.

Shedding of the EG in states of critical illness, such as shock, has been demonstrated in animal models before any fluid therapy has commenced. In mice, hemorrhagic shock was associated with a thinner pulmonary ESL, as measured by electron microscopy, and downregulation of syndecan-1 on the endothelial surface, compared to a sham model (109, 110). In a canine hemorrhagic shock model comparing different fluid interventions (111), plasma hyaluronan concentration was significantly increased across treatment groups after atraumatic blood removal, but before fluid, compared to baseline (unpublished analysis). An increase in plasma hyaluronan concentration has also been demonstrated in a rodent sepsis model, 4 h after *Escherichia coli* lipopolysaccharide infusion, where blood pressure was maintained by norepinephrine administration (112). There are limited data on EG shedding in the clinical setting before fluid therapy; however, serum syndecan-1 concentrations above healthy control levels has been demonstrated pre-hospital in human trauma patients, though the temporal relationship to fluid administration by first responders is unknown (113).

Hemodilution

Bearing in mind that alterations to the ESL may already exist in critically ill patients, there is growing evidence that administration of "clear" fluids may propagate ESL shedding. Several clinical studies in critically ill people have identified an association between volume of fluid administered and EG biomarker concentrations, including increased hyaluronan (84), syndecan (114), and heparan sulfate concentrations (115). Putting aside the confounders of inflammation and severity of illness, bolus fluid therapy may have a direct effect on the ESL via hemodilution and production of natriuretic peptides. *Ex vivo* vascular models provide important data in regards to this issue, as they exclude the effects of the varying pharmacodynamic properties of fluid types administered *in vivo*. These vascular models have shown that dilution of plasma with crystalloid reduces ESL thickness. Notably, a mathematical model derived from meta-analysis of several studies demonstrated that dilution of blood with fluid reduced vascular resistance, independent of hematocrit and COP (116). Also, the decrease in resistance caused by saline was reduced in magnitude when the vasculature was pre-treated with heparinase. Heparinase sheds heparan sulfate side-chains from proteoglycans, thus thinning the glycocalyx (117). From this, it may be inferred that the decrease in resistance caused by saline infusion is due to not only changes in hemorrheology but also loss of the ESL. Further, several studies have shown that perfusion of blood vessels with crystalloid solution increases vascular permeability. One such study showed an inverse linear relationship between albumin concentration in the perfusate and hydraulic conductivity, or permeability, of vasculature (118). Return to baseline permeability was not achieved by simply increasing the albumin concentration back to baseline levels; it required a much higher albumin concentration. This implies modification of the ESL and its affinity for albumin after crystalloid infusion. Further experiments showed that perfusion of blood vessels with plasma was more effective at restoring normal vascular permeability after crystalloid infusion (119), compared with an albumin solution, indicating that substances within plasma are important for maintaining normal transvascular fluid flux. A more recent study showed that infusion of guinea pig coronary vasculature with 0.9% saline significantly increased fluid extravasation, compared to low molecular weight (LMW) hydroxyethyl starch (HES) (Voluven®) and albumin solution (45). Pretreatment with heparinase combined with saline infusion did not yield higher fluid extravasation; stripping the EG before infusion was just as detrimental as saline infusion alone. Interestingly, no differences between fluid treatments in the appearance of the ESL were appreciated using electron microscopy. Finally, a murine hemorrhagic shock model compared 15 mL/kg of either fresh whole blood (FWB), packed red blood cells in lactated Ringer's solution (PRBC in LRS), or washed PRBC in LRS, or 75 mL/kg of plain LRS (120). Rats that received either washed PRBC or LRS

had decreased ESL thickness compared to baseline, as measured by intravital microscopy, whereas those that received either FWB or PRBC did not show a significant difference to baseline. Results were similar for change in plasma heparan sulfate concentration. Therefore, it appeared that the presence of protein within the FWB and unwashed PRBC products was effective at mitigating ESL shedding.

Natriuretic Peptides

Another mechanism of EG shedding during bolus fluid therapy is the action of natriuretic peptides on the endothelium. Atrial and brain natriuretic peptides (ANP and BNP, respectively) are released from the cardiac atria and ventricles during stretch of the myocardium (121). These peptides counteract the effects of hypervolemia by decreasing systemic vascular resistance and causing a natriuresis, among other mechanisms. Natriuretic peptides also increase vascular permeability (122, 123). A more recently discovered role of these peptides is shedding of the EG. All three major natriuretic peptides (ANP, BNP, and C-type NP) can shed the EG, as measured by increased syndecan-1 and heparan sulfate concentrations in the effluent of guinea pig coronary arteries (88, 124). These studies also demonstrated increased vascular permeability and visualized denudation of the ESL via electron microscopy.

Fast intravenous administration of isotonic crystalloid fluid may stimulate natriuretic peptide release during the bolus phase. The dose of crystalloid administered for treatment of shock far exceeds the volume remaining in circulation after redistribution. This rapid rise and fall of blood volume during a crystalloid bolus was demonstrated by Silverstein and others (7), whereby the blood volume rapidly rose by 76% during a large bolus of 0.9% saline before dissipating. Therefore, it is possible that atria may become "over-stretched" during crystalloid bolus fluid therapy and release natriuretic peptides, which may then contribute to systemic EG shedding. Two studies in human surgical patients have shown a rise in ANP in parallel with EG biomarker concentrations after fluid loading (125, 126). These studies showed a significant increase in serum syndecan-1 and hyaluronan concentrations but not heparan sulfate. One additional study showed an increase in ANP and all three EG biomarker concentrations in cardiac surgical patients; in both those undergoing cardiopulmonary bypass and those undergoing "off-pump" procedures (127). In contrast, one study in people undergoing hysterectomy ($n = 26$) showed no significant rise in BNP or biomarker concentrations (syndecan-1 and heparan sulfate) after 25 mL/kg of LRS given over 30 min during surgery (128). An additional study showed no significant rise in BNP or any EG biomarker concentrations (syndecan-1, heparan sulfate, hyaluronan) in human surgical patients or healthy volunteers during a modest fluid load of 3 mL/kg of 20% albumin, though sample size was small ($n = 15$ per group) (129). A recent canine hemorrhagic shock study did not observe a significant increase in plasma ANP concentration after 80 mL/kg of balanced isotonic crystalloid given over 20 min, however small sample size ($n = 6$) and baseline variability may have hampered the ability to detect a difference (111).

Other Considerations Related to EG Biomarker Type

One of the challenges of interpreting studies that measure EG biomarker concentrations as the primary assessment of EG shedding is the variability in choice of biomarker. Across multiple studies investigating the effect of fluid loading on the EG, it appears that hyaluronan is consistently increased immediately after a large volume of crystalloid, or synthetic colloid fluid in the setting of hypervolemia (111, 125, 126). Syndecan-1 concentration significantly increases after fluid in humans and rats (110, 125, 126, 130–132), but not in all studies (128, 133). Heparan sulfate has not been shown to significantly increase in humans (125, 126, 128) but has been shown to increase in rats (120, 130, 133). Unpicking these consistencies is difficult due to differences across species, study designs, fluid doses, timing of intervention and blood sampling, and choice of comparator (other fluid vs. no fluid vs. sham). Studies may also vary in whether or not they adjust the biomarker concentration for the effects of hemodilution, such as indexing to albumin, hemoglobin, or other tracer concentration in the blood. Although this may help to account for the different pharmacodynamics of each fluid type, and their variable dilution of blood tracer components, indexation of biomarker concentrations can create a margin of error. On closer inspection of individual studies, inconsistency has been shown within the studies themselves, showing a significant change in one biomarker but not the other (125, 126, 133). As mentioned above, the source of circulating EG biomarkers may not be restricted to the endothelium and other sources, such as the interstitium or surface of other cells, may be contributing. Therefore, a healthy sceptism should be applied to any conclusion drawn from biomarker concentrations alone.

COMPARATIVE EFFECTS OF DIFFERENT FLUID TYPES

Much of the evidence concerning EG or ESL shedding after fluid therapy concerns the use of large volumes of crystalloid fluid. Administering other fluid types that have less redistribution to the interstitium may theoretically be associated with less EG shedding. This section assesses the evidence for the comparative effect of crystalloid, synthetic colloid, and hypertonic fluids on the EG or ESL.

Isotonic Crystalloid Fluid

Multiple rodent studies have shown that administration of large volumes of crystalloid fluid for hemorrhagic shock is associated with more EG shedding, compared to fluids containing protein (109, 110, 120, 130–133). However, it is difficult to compare interventions in regards to effects on the EG in many of these studies, as cardiovascular parameters are either not closely monitored or are different between treatment groups. Shock itself, without fluid resuscitation, can cause EG shedding (109, 110, 131, 134–136), which becomes a confounder when comparing resuscitation strategies that provide inequitable blood

volume expansion. However, several key studies allow some assessment of this issue. A murine hemorrhagic shock model showed that administration of protein-poor fluids, either washed PRBCs or LRS, was associated with a thinner ESL, whereas protein-containing fluids (FWB and PRBCs) were not (120). Cardiovascular parameters after resuscitation appeared similar across these groups, based on the limited data available. Another murine hemorrhagic shock model compared seven different fluid strategies: 15 mL/kg of FWB, PRBC, fresh frozen plasma (FFP) or 5% albumin, 8 mL/kg of 3% saline, 45 mL/kg of 0.9% saline, or 75 mL/kg of LRS (130). Shock index, usually defined by heart rate divided by systolic blood pressure, was compared before hemorrhage and immediately after fluid resuscitation within each fluid group. Rats that received either 5% albumin, LRS, 3% saline, or 0.9% saline had a significantly increased shock index after fluid resuscitation, whereas rats that received FWB, PRBC, and FFP showed no change in shock index. When comparing only the fluid types that did not resolve shock, based on shock index, rats that received 5% albumin had higher ESL thickness and lower EG biomarker concentrations, compared to the crystalloid groups. Finally, a murine hemorrhagic shock model used a blood pressure-targeted resuscitation method for comparing crystalloid fluid with plasma (109). Administration of LRS was associated with a thinner ESL, visualized on electron microscopy, and decreased endothelial expression of syndecan-1, compared to administration of plasma.

There is a scarcity of "large animal" models, or those including pigs, sheep, and dogs, that have assessed ESL shedding after fluid resuscitation. This may be partially due to a limitation on validated assays available for measuring glycocalyx biomarkers across these species. Current commercially available validated options for assessing EG shedding are restricted to circulating hyaluronan concentration. A canine hemorrhagic shock model did not detect a significant difference in plasma hyaluronan concentrations when comparing dogs that received 20 mL/kg of FWB ($n = 6$) with those that received 80 mL/kg of Plasmalyte-148® ($n = 6$) (111). Other differences in parameters were seen between the crystalloid and colloid fluid groups in this study, which is discussed further below. In an ovine endotoxemia model, a pressure-targeted resuscitation method using vasopressor therapy was used to compare either norepinephrine alone or 0.9% saline (40 mL/kg) in combination with norepinephrine (137). Although there was no comparison to resuscitation with a protein-containing fluid, the comparison of crystalloid fluid to *no* fluid in the setting of sepsis provided interesting results. There was no significant difference in serum hyaluronan concentrations between groups over time, though sheep that received 0.9% saline showed a greater rate of increase in this biomarker. This greater increase was not observed directly after the fluid bolus, like in the aforementioned canine study, but beyond 6 h, which may have been related to worsening septic shock in this group. Atrial natriuretic peptide was significantly higher at the end of the fluid bolus in the sheep that received fluid (see previous discussion on natriuretic peptides). Detection of between-group differences was also likely affected by small sample size in this study ($n = 8$ per group), similar to the study in dogs.

Synthetic Colloid Fluids

Given that crystalloid fluids generally require a larger volume to expand circulating blood volume to the same extent as colloid fluids (6–9), crystalloids cause greater hemodilution during the fluid bolus and, potentially, greater natriuretic peptide release. This begs the question if administration of colloid fluids causes less EG shedding than crystalloid fluid. Two main types of synthetic colloid are currently in use: HES and gelatin products. The aforementioned canine hemorrhagic shock study included both of these fluid types at 20 mL/kg, as comparator fluids to 80 mL/kg of Plasmalyte-148® (111). Dogs administered HES had significantly lower plasma hyaluronan concentration immediately after the fluid bolus, compared to both FWB and crystalloid groups. In contrast, the group that received 4% succinylated gelatin had significantly increased plasma hyaluronan concentration 40 and 100 min after the end of the fluid bolus, compared to FWB. Given that inflammation may cause EG shedding, these differential effects observed between these two colloids may be due to release of inflammatory mediators; HES has been associated with mitigation of inflammation (138–141) whereas gelatin has been associated with pro-inflammatory effects (142). However, there were no differences in plasma concentrations of inflammatory mediators between the two colloid groups in this study (111). Therefore, the effect of gelatin on hyaluronan shedding may be a direct effect of the fluid, rather than pro-inflammatory effects, such as washout of the interstitium. Another hemorrhagic shock study in rats replaced the shed volume with crystalloid, at either shed volume, two times shed volume, or three times shed volume, or shed volume with HES ($n = 6$ per group) (141). This study did not identify any significant differences between groups in response of blood pressure to fluid resuscitation, organ syndecan-1 expression, or circulating syndecan-1 concentration. A hemorrhagic shock, stroke volume-targeted resuscitation model in pigs compared balanced crystalloid to HES and found no differences in post-fluid serum syndecan-1 or glypican concentrations (6). Blood was sampled 120 min after commencement of fluids, therefore any peaks in EG biomarker shedding may have been missed. Given the limited evidence for different effects of colloid fluids on the EG or ESL, compared to crystalloids, a conclusion cannot be currently drawn.

Hypertonic Crystalloid Fluids

Hypertonic solutions exert immunomodulatory effects both in *in vitro* and animal model studies, including decreased leucocyte response to pro-inflammatory stimuli or circulatory shock states, when compared to other fluid types (143–156). Administration of hypertonic saline to human trauma patients also reduced inflammatory biomarker concentration, compared to isotonic saline (157, 158). Several studies have also shown a reduction in vascular leakage of macromolecules (147, 151, 155). Given these effects, it is possible that hypertonic solutions may have a beneficial effect in regards to reducing ESL shedding.

In the rodent hemorrhagic shock model previously discussed comparing many different type of fluids, rats that received 8 mL/kg of 3% saline had a lower increase from baseline in plasma heparan sulfate concentration, compared to both isotonic crystalloid groups (45 mL/kg of 0.9% saline or 75 mL/kg of LRS), and a lower loss of ESL thickness (130). This difference was despite a persistence of an elevated shock index and hyperlactatemia after resuscitation with 3% saline. Therefore, although hypertonic saline may have had less impact on the EG, it may have also provided inadequate fluid resuscitation. A preliminary randomized clinical trial in people with suspected sepsis could not demonstrate a difference between groups in hyaluronan concentrations after treatment allocation of either 5 mL/kg of 3% saline or 10 mL/kg of 0.9% saline (86). Serum syndecan-1 concentration decreased after 0.9% saline, compared to baseline, whereas serum syndecan-1 concentration did not change after 3% saline. Though this significant difference between groups may reflect hemodilution, as twice the volume of 0.9% saline was administered, this was not reflected in differences in hemoglobin concentration. It is unclear what the clinical significance is of this subtle difference in change in serum syndecan-1 concentration, whether it reflects more syndecan-1 shedding in the hypertonic saline group or not. Limitations of this study included a low severity of illness and small sample size, and further studies are needed to clarify the effects of hypertonic solutions on the EG.

GLYCOPROTECTIVE THERAPIES

The clinical relevance of ESL shedding due to fast or large-volume fluid administration is yet to be determined. This type of fluid administration can cause shedding of the ESL, which may propagate microcirculatory dysfunction, inflammation, and procoagulation. Therefore, there has been much interest developing in "glycoprotective" fluid strategies or adjunctive therapies during the resuscitation phase.

Restricting or Avoiding Fluid

Blood volume expansion is the cornerstone of managing circulatory shock, with some types of shock an exception such as cardiogenic shock. Conventionally, this is achieved by administering large (more than 20 mL/kg) volumes of crystalloid fluid intravenously as rapidly as possible, or as a bolus (159, 160). This serves to increase cardiac preload and improve cardiac output. The need for this intervention is intuitive for shock caused by hypovolemia; however, some types of shock have a component of vasodilation and microcirculatory dysfunction. This includes states of shock due to a systemic inflammatory response, such as sepsis and blunt trauma. For these types of shock, improvement of macrohemodynamic variables, such as cardiac output and blood pressure, may not improve microcirculatory blood flow in a linear way. This is particularly pertinent to septic shock, where the role of fluid bolus therapy has been called into question, with a movement toward early vasopressor therapy instead (161, 162). Further to the lack of improvement in microcirculatory flow, it has been suggested that fluid bolus therapy in sepsis can propagate vasodilation, due to endothelial shear stress, release of nitric oxide, and direct vasodilatory effects of natriuretic peptides. This may contribute to some patients becoming refractory to vasopressor therapy. In an ovine endotoxemia model, administration of 40 mL/kg of 0.9% saline was associated with a significantly higher dose of noradrenaline subsequently administered in order to maintain blood pressure, compared to sheep that received only noradrenaline (137). Given the concern that bolus fluids may cause harm in sepsis, a preliminary randomized clinical trial was completed demonstrating feasibility of restricting crystalloid fluid early in the treatment of sepsis in people (163). Following on from this, a large multi-center human randomized clinical trial is underway to compare a restrictive fluid strategy with a more liberal one in people with early sepsis (164).

It is much less known if restricting crystalloid fluid in other types of shock may be beneficial. In the setting of human trauma, discussion concerning restrictive crystalloid fluid strategies focuses on delayed resuscitation or permissive hypotension in order to avoid clot disruption and dilutional coagulopathy before definitive hemostasis (4, 165). Although animal models have shown that fluid resuscitation is likely beneficial for severe uncontrolled hemorrhage, it increases the risk of mortality in lower grades of severity of bleeding, compared to not administering any fluid (166). Hypotensive resuscitation, in parallel with lower volumes of administered fluids, is also associated with a reduced risk of mortality in human trauma patients (167, 168), though the evidence is mixed (169). This benefit is likely related to improved coagulation and clot stability; it is unknown if there are also benefits associated with reducing endothelial dysfunction. Currently, the recommendation in human trauma medicine is for limitation of "clear" fluid and early, yet judicious, administration of blood products. This includes packed red blood cells, plasma, and platelets in parallel during resuscitation. The early administration of plasma may not only serve to limit dilutional coagulopathy but also assist with repairing the ESL. It is difficult to translate this practice to veterinary medicine, given the cost of transfusion, limited availability, and variability in blood banking practices. Given there are many factors entering into the cost to benefit assessment of administering plasma or albumin products to individuals, theoretical benefits of plasma for the ESL are of lesser importance, until more is known. Also, caution should be applied when restricting crystalloid fluid to any patient with shock, as the benefits of a restrictive strategy may be only relevant to certain patient populations, such as sepsis. This concept was highlighted by a recent randomized clinical trial in human surgical patients whereby participants randomized to receive a restrictive fluid strategy had a significantly higher rate of acute kidney injury and surgical site infection, compared to those randomized to a liberal fluid strategy (170).

Slowing Fluid Administration

Fast fluid administration serves to rapidly improve clinical signs and macrohemodynamic variables, and has been the bread-and-butter of emergency and critical care medicine for decades. However, normalization of macrohemodynamic variables in people does not always translate to improved

microcirculatory flow (47–49, 51). This is termed a lack of hemodynamic coherence (171). Intravenous fluid delivered rapidly during the stabilization phase may be contributing to persistence of disturbed microcirculatory flow. When viewing the microcirculation using sidestream dark field microscopy during anesthesia in pigs, fast fluid administration (20 mL/kg/hr) for 3 h was associated with development of heterogeneity in capillary blood flow, compared to "standard" anesthesia fluid rates (5 mL/kg/hr) (172). Although a direct relationship between estimated ESL thickness and microcirculatory flow has not been established in the clinical setting (46), it is possible that amplification of ESL shedding caused by fast fluid administration may be contributing to microcirculatory dysfunction. It is possible that slower fluid administration may achieve the same resuscitation end-points while avoiding some of these deleterious effects on the endothelium. This concept has been explored in a handful of studies. In a rodent model where 40% of the blood volume was removed by atraumatic hemorrhage, rats were assigned to receive no fluid, rapid fluid (0.9% saline at three times shed volume over 30 min), or slow fluid (0.9% saline at three times shed volume over 12 h) (173). Rats in the fast fluid group showed higher inflammatory cytokine concentrations early in the study and some markers of worse outcome over the latter part of the study, including lower mean arterial blood pressure, higher blood glucose and lactate concentrations, and an increase in markers of lung injury, compared to rats in the slow fluid group. As the rats were euthanased after 24 h, it is unknown how their recovery progressed. In a human open randomized clinical trial, including 50 surgical and 16 septic patients, no significant difference was found in estimated ESL thickness between patients that received fast crystalloid administration (5–10 min) and slow crystalloid administration (20–30 min) (48). However, an overall decrease in estimated ESL thickness after fluid administration was observed. Given that there is some evidence that rapid fluid administration (i.e., within 10 min) may not provide any clinical benefit over slower fluid administration (i.e., within 20 to 60 min) (8, 174), larger clinical trials are justified to explore effects of fluid rate on the microcirculation and clinical outcomes.

Choice of Clear Fluid Type

Intense ongoing debate surrounds the choice of fluid for critically ill patients, including crystalloid, synthetic colloid, and protein-containing solutions. These conversations surround relative fluid effectiveness and adverse effects, many of which are still yet to be fully elucidated for clinical relevance in certain species or disease subsets. Adding in the potential benefit or detriment of certain fluid types to preservation of the ESL and optimizing microcirculation is still premature. Bearing that in mind, the current evidence supports mitigating hemodilution and avoiding hypervolemia in order to optimize ESL recovery. There is theoretical benefit for the ESL to the use of protein-containing solutions, such as plasma and albumin, rather than "clear" fluids, but this must be carefully considered against any detrimental effects of blood products, including financial cost. At this stage, no clear recommendation can be made for veterinary medicine, and more clinical research is required.

Adjunctive Therapies

Many drugs have been explored as to their protective or resurrecting actions for the ESL and have been reviewed in detail elsewhere (175, 176). These therapies may become viable in the future for use during the optimization and stabilization phase of fluid resuscitation (177). Therapies that are in current use in veterinary medicine that have been shown to have beneficial effects on the EG or ESL include albumin solution, plasma, hydrocortisone, heparin, and N-acetylcysteine.

CONCLUSIONS

The coating of endothelium by the EG and its associated molecules serves many functions in the body, both intact and when denuded. Infusion of large volumes of fluid causes disruption of this layer, which may propagate interstitial edema and inflammation. There is some evidence that slow fluid administration or restricting the volume of crystalloid fluid for shock resuscitation may benefit the patient. Exactly how to do this and for which patient subset this strategy benefits in veterinary medicine remains to be identified. Clinical veterinary research assessing the effect of glycoprotective therapy or strategies is currently limited by a lack of validated EG biomarker assays and affordable, reliable technology for estimating ESL thickness *in vivo*. Further work is required on developing validated, reliable EG biomarker assays and determining the relationship between these biomarkers and shedding of the ESL *in vivo*, especially for dogs and cats. Despite these current limitations, future research directions should also focus on strategies limiting crystalloid fluid volumes, especially in the setting of sepsis and early vasopressor drug therapy.

AUTHOR CONTRIBUTIONS

LS: preparation of manuscript and final approval. DH: revision of manuscript and final approval. Both authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Fluid Therapy and the Microcirculation in Health and Critical Illness

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Fluid selection and administration during shock is typically guided by consideration of macrovascular abnormalities and resuscitative targets (perfusion parameters, heart rate, blood pressure, cardiac output). However, the microcirculatory unit (comprised of arterioles, true capillaries, and venules) is vital for the effective delivery of oxygen and nutrients to cells and removal of waste products from the tissue beds. Given that the microcirculation is subject to both systemic and local control, there is potential for functional changes and impacts on tissue perfusion that are not reflected by macrocirculatory parameters. This chapter will present an overview of the structure, function and regulation of the microcirculation and endothelial surface layer in health and shock states such as trauma, hemorrhage and sepsis. This will set the stage for consideration of how these microcirculatory characteristics, and the potential disconnect between micro- and macrovascular perfusion, may affect decisions related to acute fluid therapy (fluid type, amount, and rate) and monitoring of resuscitative efforts. Available evidence for the impact of various fluids and resuscitative strategies on the microcirculation will also be reviewed.

Keywords: microcirculation, macrocirculation, shock, sepsis, hemorrhage, glycocalyx

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INTRODUCTION

Given the complex and multi-faceted nature of emergent and critical disease processes, determination of optimal approaches to fluid resuscitation continues to be a challenge for both human and veterinary medicine. Further complicating the ideal approach is determining how best to initially assess the severity of systemic compromise and gauge response to therapy. Traditionally, monitoring of a patient's hemodynamic state has been conducted at the macrovascular level by monitoring heart rate, respiratory rate, blood pressure, oxygen content and lactate, among other parameters. While these parameters may reflect systemic cardiovascular regulation, they do not necessarily indicate what is occurring at the level of the microvasculature. As the microcirculation is ultimately the conduit for delivery of oxygen and nutrients to tissues, it represents a relatively uncharted avenue of exploration to help enhance our understanding of disease processes like trauma and sepsis, its impact on tissue perfusion, as well as new ways to monitor response to therapy.

The goal of this manuscript will be to explore the structure, function, and regulation of the microcirculation, both in health and in response to disease processes like traumatic hemorrhage (representing hypovolemia and systemic vasoconstriction) and sepsis (representing a vasodilatory and maldistributive process). Finally, there will be consideration of modalities for assessing the microcirculation and tissue perfusion.

STRUCTURE AND FUNCTION OF THE MICROCIRCULATION

The microcirculatory unit is comprised of arterioles feeding into a capillary bed that is drained by venules (**Figure 1**). The feeder arterioles are highly muscular throughout their length, while the terminal metarterioles have intermittent bands of smooth muscle. True capillaries have walls that lack musculature and are one endothelial cell thick and attached to a basement membrane. A precapillary sphincter is located between the arteriole and the capillary bed. Arterioles and venules in the microcirculation generally have a diameter < 100 microns, while the capillaries are < 10 microns in diameter (1). There are also shunt vessels that allow arterial blood to completely bypass the associated microcirculatory unit, as dictated by arteriolar and precapillary sphincter tone (1). The vascular endothelial surface layer (ESL) also plays a pivotal role in health and disease; this is the intimal surface of blood vessels containing the endothelial glycocalyx and associated components from the endothelial cells and plasma (2, 3). The ESL ranges from 200 nm to 2 μm in thickness and comprises up to 25% of the vascular space (4). The glycocalyx is a complex carbohydrate rich gel-like layer that serves as a barrier between the vessel wall and the blood (2, 5, 6) and has an overall negative charge. It contains membrane-bound proteoglycans, secreted glycosaminoglycans, sialic acid-containing glycoproteins, and glycolipids that are associated with the vascular endothelial surface (7). Proteins within the plasma, such as albumin and antithrombin, are also contained within the glycocalyx (7–9). The primary goals of the ESL are to maintain the vascular permeability barrier, modulate nitric oxide produced in response to shear stress, retain protective enzymes such as superoxide dismutase, contain factors that inhibit coagulation such as antithrombin, tissue factor pathway inhibitor and protein C, assist with mechanotransduction, and prevent leukocyte adhesion and binding of ligands to control local inflammation (3, 10). Recent discoveries in the ESL have contributed to the revised version of the Starling principle of transvascular fluid flux (11). Further details about the ESL are described in "Resuscitative Fluid Therapy and the Endothelial Surface Layer" found elsewhere in this "Fluid Therapy in Small Animals" series.

Altogether, the microcirculation represents the largest vascular surface area in the body and is vital for the effective delivery of nutrients to the cells and removal of waste products from the tissue beds (1). Both systemic and local regulation of blood flow through these units, as well as maintenance of the ESL, are essential to maintain adequate perfusion and match metabolic demand to oxygen/nutrient delivery.

MICROVASCULAR PERFUSION—SYSTEMIC CONTROL

Vascular tone can be influenced by numerous chemical mediators in the circulation, such as catecholamines, endothelin and thromboxane (**Table 1**). Catecholamines are important (predominantly) vasoconstrictor agents released in large amounts when the sympathetic nervous system is activated. This occurs via central nervous system control in response to baroreceptors and chemoreceptors in the aortic arch and carotid sinuses (12). Baroreceptors respond to changes in vessel wall distension and chemoreceptors respond to hypoxia, hypercapnia or acidemia with associated modulation in vascular tone. These effects are most important once the systemic arterial pressure drops below 80 mmHg; they attempt to maintain perfusion in individual capillary beds despite decreased systemic blood pressure (12).

It is important to note sympathetic innervation exists for the arterial tree and much of the venous system but is not present down to the level of the capillaries. The absence of innervation and musculature in the true capillaries means flow through each capillary bed is regulated by the hemodynamic pressures generated between the precapillary sphincter and the post capillary venules. A single capillary bed can be fed by multiple arterioles, a situation that allows flow through the capillary bed to increase by 200–500% without any significant change in the overall arteriolar pressure (13). This can help to preserve microcirculatory flow to specific tissue beds during periods of transient systemic hypotension.

Maintenance of vascular tone is not the only factor influencing arterial blood pressure and tissue perfusion. Vascular volume also contributes to maintenance of appropriate blood pressure and tissue perfusion. In normal animals, the renin-angiotensin-aldosterone system is integral in maintaining appropriate blood volume, as well as contributing to systemic vascular tone (4). Angiotensin II acts on vascular smooth muscle to cause vasoconstriction and in the proximal tubules it causes sodium and water retention, leading to increased blood volume and arterial pressure (14). Angiotensin also causes the release of aldosterone and vasopressin, thus promoting vasoconstriction and water retention (14).

Systemically acting vasodilators include the kinins, adrenomedullin and atrial natriuretic peptide (ANP). The kinins include bradykinin and l-lysyl-bradykinin and are activated by the kallikreins. They typically regulate blood flow at the tissue level but can also be found circulating in the bloodstream. In addition to causing arteriolar dilation, bradykinin increases capillary permeability, thereby increasing the delivery of nutrients to the tissue bed (15). Histamine, which is released when tissues are damaged or in allergic reactions, also acts as a vasodilator and increases capillary permeability. Adrenomedullin increases the production of NO while ANP acts to antagonize numerous vasoconstrictor agents, both exerting their influence on the vascular tone indirectly (15).

These systemic regulators are responsible for controlling delivery of blood to the precapillary sphincter across different tissue beds. Once blood arrives at the capillary bed, local

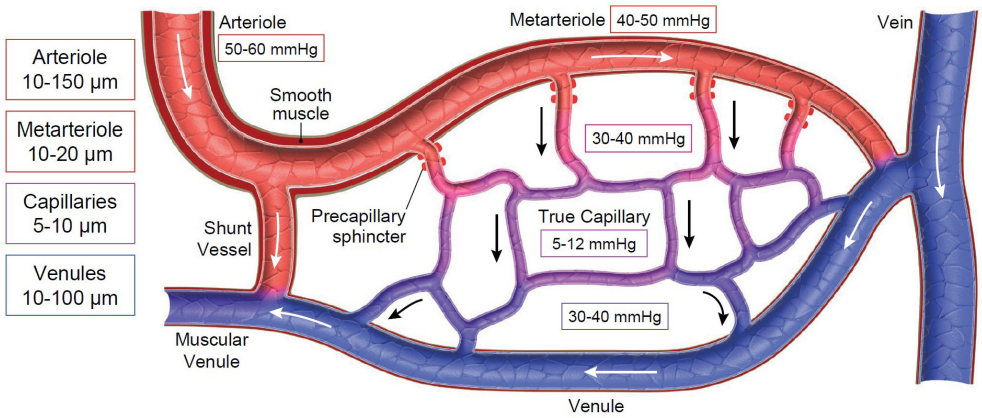

FIGURE 1 | Schematic of the microcirculation. Boxes on the left represent ranges of vessel diameters at varying levels of the microcirculation. Boxes throughout the diagram represent the average interstitial (tissue) oxygen tension (P_tO_2). Arrows represent direction of blood flow across the microcirculatory unit.

TABLE 1 | Endogenous chemical mediators of vascular smooth muscle tone.

Vasoconstriction	Vasodilation
Thromboxane A2	Prostacyclin
Endothelins	Endothelium-derived hyperpolarizing factor
Endothelium-derived constricting factor 1	Nitric oxide
Endothelium-derived constricting factor 1	Histamine
Vasopressin	Kinins
Angiotensin II	Carbon dioxide
Epinephrine/Norepinephrine	Elevated tissue potassium, ADP, adenosine
Hypothermia	Hyperthermia
Hyperoxia	Hypoxia
Alkalosis	Acidosis

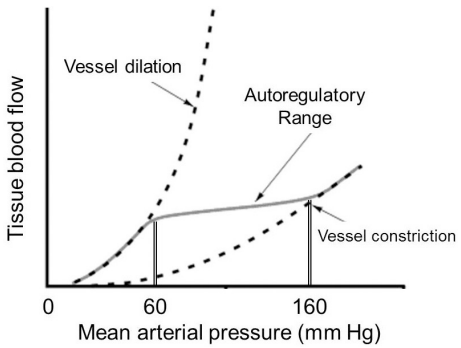

FIGURE 2 | Curve reflecting tissue autoregulation for maintaining consistent blood flow across varying systemic perfusion pressures.

regulatory mechanisms act to maintain flow through the capillary bed, sometimes independent of systemic changes to perfusion (15).

MICROVASCULAR PERFUSION—LOCAL CONTROL

Basal tissue bed requirements vary based on their metabolic rate, nutrient availability and accumulation of waste products. Given that each capillary bed has unique requirements that may change independent of nearby capillary beds or systemic tissue needs, there are many local regulators of microcirculatory flow (**Table 1**). Typically, these changes in perfusion occur at the level of the precapillary sphincter. Independent regulation of flow based on local tissue needs results in selective capillary perfusion and the potential for microcirculatory shunting. Given the expansive nature of the capillary circulation, cardiac output would be insufficient to maintain forward flow if every capillary bed were to open simultaneously. Thus, the ability to adjust capillary perfusion through local and systemic changes is essential for modulating cardiac workload (15).

Rapid control of microcirculatory flow is mediated at a local level through autoregulation. One major mechanism is flow autoregulation, which allows maintenance of consistent capillary blood flow over a wide range of arterial perfusion pressure. This is achieved through vascular stretch receptors which respond to changes in peripheral pressure. Increases in vascular pressure trigger increased tone of the precapillary sphincter to mute transmission of that pressure though the capillary circuit (16). The opposite happens with a fall in peripheral pressure. This mechanism is effective for maintaining consistent flow over a perfusion pressure (mean arterial pressure) of 60–160 mm Hg and occurs independent of any neurohormonal input (**Figure 2**).

Changes in local metabolic demand can also have a significant impact on local control of blood flow. Understandably, by-products of increased metabolic activity, such as carbon dioxide, lactate, and hydrogen ion will trigger vasodilation to enhance local blood flow and improve oxygen/nutrient delivery. While

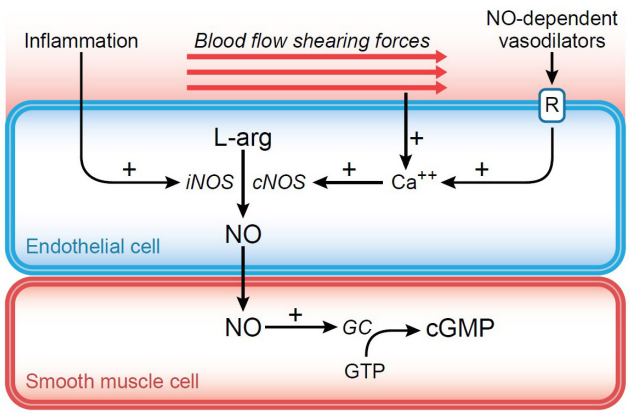

FIGURE 3 | Diagram representing the impact of shear force generated against the endothelium. Through mechanotransduction, intracellular calcium is increased leading to increased nitric oxide (NO) production from stimulation of constitutive nitric oxide synthetase (cNOS). NO diffuses into surrounding smooth muscle cell causing activation of guanylyl cyclase (GC) and conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). The resulting decrease in cytosolic calcium causes relaxation of vascular smooth muscle and vasodilation.

these metabolites are produced downstream, the countercurrent flow between arterioles and venules allows them to be "sensed" at the level of the precapillary sphincter and alter inward flow (16). In addition, inter-cell and local neural pathways allow conduction of signals from capillary endothelium and venular smooth muscle in response to these signals (16).

Local levels of oxygen tension will also affect microcirculatory regulation. Under normal circumstances, capillary blood has a significantly lower PO_2 (5–12 mm Hg) compared to arteriolar blood (~60 mm Hg). This occurs because of early off-loading in precapillary tissues, as well as endothelial consumption and countercurrent exchange with venous flow (16). An increase in precapillary tissue PO_2 will promote vasoconstriction, whereas a decrease will result in vasodilation, largely through release of nitric oxide (NO). In addition to this role, NO has an impact on microvascular tone in a number of other circumstances (16). Normally, the constitutive form of nitric oxide synthetase (cNOS) is responsible for maintaining a basal level of NO and modulating vascular tone. Further, an increase in blood viscosity, which occurs in diseases such as polycythemia vera or severe hemoconcentration, results in elevated shear stress on the vascular endothelium. Through mechanotransduction shear stress serves to increase cNOS activity, resulting in increased release of NO, and associated vasodilation (**Figure 3**). The opposite would occur in severe anemia/hemodilution with significant reduction in red cell mass and blood viscosity (17). The inducible form of nitric oxide synthetase (iNOS) can be produced by the endothelial cells when triggered by the inflammatory cascade. Prostacyclin-induced vasodilation may also play a role in the normal response to hypoxia, especially when NO is blocked there is shear stress (18).

MICROVASCULAR CHANGES WITH TRAUMA AND HEMORRHAGIC SHOCK

Given the complex nature of the microcirculation and its multifactorial regulation, it stands to reason that microvascular perfusion will be altered in varying ways in response to disease states. In the face of tissue injury, hypotension, and impaired oxygen delivery, it can be expected that there will be activation of both systemic and local compensatory and pathological mechanisms. While some of this response has already been described in a general sense, what follows is more specifically related to microvascular changes secondary to trauma and hemorrhage.

The initial systemic response to tissue trauma, pain, and hemorrhage is largely driven by the sympathetic nervous system leading to release of epinephrine and norepinephrine. The resulting influx of catecholamines will promote vasoconstriction, particularly in the large arterioles (70–150 μm) supplying skeletal muscle (19). Smaller arterioles (10–25 μm) have a more varied response, with constriction to some beds and dilation in others. This next level allows for finer regulation of microcirculatory flow based on metabolic demand and the "essential nature" of the associated organ/tissue bed (e.g., heart and brain).

Local factors caused by trauma and hemorrhage will also cause changes at the level of the small arterioles. Decreased oxygen delivery and tissue hypoxia will tend to cause vasodilation. However, this is offset by inhibition of eNOS (and thereby release of NO) in the early stages of trauma/hemorrhage. With time, however, there is upregulation of iNOS (from both tissue damage and inflammatory mediators) and more tendency for vasodilation (20). In addition, tissue injury and the inflammatory response will promote release of assorted vasoactive mediators with mixed effects. Progressive acidosis and accumulation of cellular metabolites (particularly in the terminal stages of shock) will tend to promote vasodilation and serve to undo systemic vasoconstrictive efforts. Despite the vasodilation, the decrease in driving pressure in the face of hypotension ultimately leads to stagnation of blood flow.

It is also important to consider the potential role of the venous circulation on microvascular perfusion. In the initial response to trauma and hemorrhage, catecholamine-induced venoconstriction, albeit limited, serves to decrease venous capacitance and encourage return of blood to the heart. However, as shock progresses there will be a general relaxation (through similar mechanisms described above), and pooling of blood in venous circulation. This downstream stagnation can then negatively impact blood flow across the capillary bed.

There are several other factors that can contribute to impaired microcirculatory flow. With trauma, inflammation, and shock there can be significant swelling of vascular endothelial cells secondary to increased membrane permeability, acidosis, and impaired electrolyte transport from failure of ATP-dependent channels (21). Given capillary luminal size, further reduction from endothelial swelling can have a significant negative impact on capillary blood flow. Endothelial edema causes decreased release of prostacyclin and NO and increased release of endothelin and thromboxane; the net effect of which is

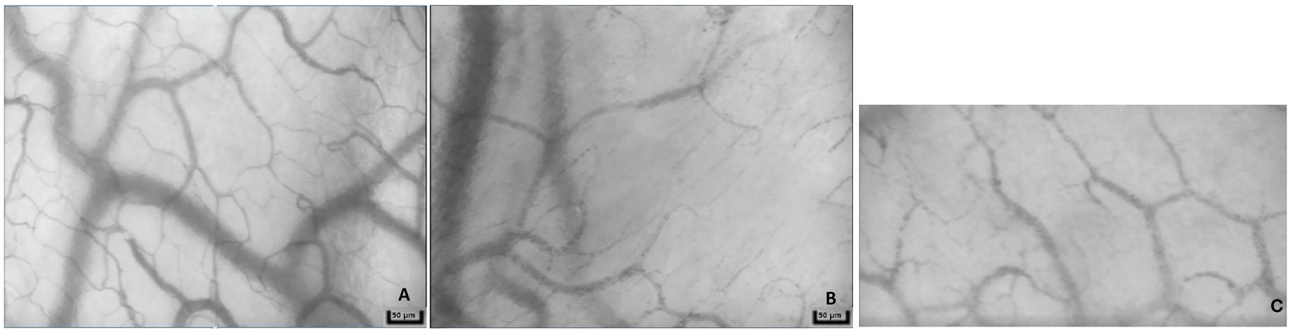

FIGURE 4 | Representative images from a sidestream dark-field microscopy device from a healthy dog **(A)**, dog in hemorrhagic shock **(B)**, and dog in septic shock **(C)**. Note the decreased density of capillaries in patients with shock.

upstream vasoconstriction and a further reduction in capillary flow. Another contributing factor can be decreased red blood cell (RBC) deformability secondary to oxidative injury, ATP depletion, cell membrane injury, and cellular dehydration (21). As RBCs are typically slightly larger than the capillary lumen, folding is necessary for them to effectively move through the microcirculation. Impaired deformability, along with aggregation, can lead to capillary plugging, or shearing injury/destruction of RBCs. Along similar lines, increased leukocyte rigidity, activation, and endothelial adherence can also result in arteriolar and capillary plugging. Lastly, microthrombi formed secondary to tissue/endothelial injury, inflammatory response and hypercoagulability can lodge at various levels of the microcirculation and impede downstream flow.

These upstream and downstream effects will ultimately serve to impact capillary flow and delivery of oxygen and nutrients. Vasoconstriction will lead to shunting of blood away from capillary circulation (decrease vessel number) and hypotension, vasodilation, and obstruction will lead to stagnation (decreased flow). In addition, these abnormalities can persist for an extended period after resuscitation has been achieved, even when macrovascular parameters have been normalized (21, 22).

Shedding of the endothelial glycocalyx has been seen in experimental rodent models of non-traumatic hemorrhagic shock, although the changes are independent of increased vascular endothelial permeability (23–25).

MICROVASCULAR CHANGES WITH SEPSIS

The pathophysiological syndrome of sepsis characterized by the progression of illness severity and potentially culminating in septic shock (26). Septic shock is described in human medicine as the presence of refractory hypotension, hyperlactatemia, and organ dysfunction that persists despite aggressive fluid resuscitation (27). The rapid progression from sepsis to septic shock and organ dysfunction is poorly understood; profound changes in the macro- and microcirculation are believed to contribute to the development of organ failure and subsequent death (28–31). Microcirculatory alterations include a decreased microvascular density and perfusion along with increased capillary flow heterogeneity (**Figure 4C** and **Supplementary Video 3**) (28, 29, 32). These changes have been found to precede macrocirculatory changes in septic humans and microcirculatory improvement has also been correlated with improved survival (28, 29, 32, 33). Early microcirculatory changes were a stronger predictor of outcome than any macrocirculatory variable in septic human patients (34).

Various factors likely contribute to the microcirculatory derangements in septic patients, including hypovolemia, endothelial cell dysfunction secondary to adhesion molecule expression, increased white blood cell adhesion, degradation of the endothelial glycocalyx, connexin uncoupling, vascular hyperpermeability, formation and deposition of microthrombi, loss of vasomotor autoregulation and reactivity, changes in local perfusion pressure and flow, and shunting of oxygen to hyperperfused capillary beds (35).

The sublingual microcirculatory derangements appear to correlate with microcirculatory changes in other organs such as the intestines and kidneys in experimental and clinical studies (36–38). Microcirculatory changes in healthy, anesthetized dogs correlate with macrocirculatory measurements of perfusion, although dogs with hemorrhagic shock do not maintain this hemodynamic coherence (39–41). Correlations in septic dogs has not yet been published.

The degraded glycocalyx layer becomes thin and sparse during sepsis, thus enabling plasma proteins and fluid to move across the vascular wall and into the interstitium (42, 43). Degradation of the glycocalyx likely occurs secondary to inflammation and increased circulating "sheddases" such as metalloproteinases, heparinase, and hyaluronidase which are activated by reactive oxygen species and proinflammatory cytokines (44). Specific changes to the endothelial glycocalyx of the lung in septic rodent models include peeling away from the endothelial surface and form spherical bodies that are visualized at the site of damage (45). An decrease in the thickness of the endothelial surface layer was seen in human patients suffering from sepsis and correlated with severity of critical illness. However, there was not an association between this thickness and microcirculatory parameters such as flow index and the proportion of perfused vessels (46).

MONITORING OF THE MICROCIRCULATION VS. MACROCIRCULATION

There is mounting evidence in human medicine to suggest that goal directed therapy aimed at maximizing macrocirculatory parameters may not improve outcome (47–49). Despite preservation of total blood flow to organs, heterogeneity of microcirculatory flow can lead to hypoxic zones (29, 50). Several techniques have now been developed to assess the microcirculation to investigate its role as a diagnostic, prognostic, and monitoring tool, including laser Doppler, near-infrared spectroscopy, and videomicroscopy (51). As mentioned above, macrocirculatory hypoperfusion is associated with microcirculatory derangements; however, dysfunction of the microcirculation may occur despite normal macrocirculatory indices. This loss of hemodynamic coherence can lead to hyperlactatemia and acidemia despite normal perfusion parameters (also known as cryptic shock) (52). When patients are in shock, normalization of cardiovascular parameters may not equate to improvements in microcirculatory perfusion, as evidenced in both clinical and experimental studies (22, 29, 32, 34, 53). There are four possible mechanisms for this loss of hemodynamic coherence: (1) increased microcirculatory heterogeneity of perfusion (i.e., secondary to inflammatory cytokines), (2) hemodilution from non-oxygen carrying intravenous fluids, thus decreasing hematocrit and oxygen content, (3) microcirculatory vasoconstriction or tamponade from endogenous/exogenous vasopressors and/or increased venous pressure, ad (4) interstitial edema of tissues secondary to endothelial and glycocalyx damage (i.e., secondary to inflammation or excessive fluid therapy) (54). In this regard, direct assessment of microcirculatory flow, such as with videomicroscopy, could be better suited to determine the presence of derangements, as well as response to fluid resuscitation.

Techniques like side stream dark field (SDF) and incident dark field (IDF) microscopy allow direct imaging of the microcirculation with the ability to quantify vessel density as well as assess quality of flow (55). Both of these technologies involve a hand-held device that emits green light (530 nm) which is absorbed by the hemoglobin of erythrocytes. These illuminated red blood cells show up as a dark density flowing through the microcirculation, resulting in a real-time magnified video with resolution to allow detection of true capillaries (**Figures 4A–C**, **Supplementary Videos 1**–**3**). Where they differ is how the light is emitted and received by the device, with reported differences in image quality and magnification (55). Analysis of the resulting videos generates parameters including total vessel density (TVD), proportion of perfused vessels (PPV), perfused vessel density (PVD), and microvascular flow index (MFI) which reflect the quantity and quality of microvascular flow. In order to allow a more consistent approach to microvascular analysis, consensus criteria for the acquisition and analysis of microcirculatory images using have been established (56).

Despite the availability of direct microvascular imaging for two decades and some evidence in veterinary medicine, (39, 40) it has still not become a standard in monitoring response to fluid therapy. Largely this has to do with some of the limitations of these technologies. The camera is expensive and not widely available. Because of the need for light to transmit and reflect back, only mucosal or serosal surfaces can be used for visualization, and areas with keratinized epithelium or significant pigmentation cannot be examined with this technique. In order to generate diagnostic quality videos for analysis, sufficient pressure has to be applied to the tissue, while avoiding excessive compression of the microvasculature (56). While significant steps have been made toward automating the vascular analysis (previously it was largely a manual effort taking over 1 h per video), accuracy of vessel assignment used for automated calculations remains a challenge. This can result in inconsistency and variability of results. Therefore, while microvascular imaging has significant potential to aid in guiding response to fluid therapy, further refinement of automated analysis and increased availability is needed before its use can become more commonplace.

There are two primary methods for assessing the integrity of the endothelial glycocalyx: measurement of shed glycocalyx components in the plasma or serum (i.e., glycosaminoglycans such as hyaluronan and proteoglycan ectodomains such as syndecan-1) and use of imaging techniques that can be done *in vivo* or *ex vivo*. Damage to the ESL and shedding of the glycocalyx has been shown to occur in a multitude of serious illnesses; the degree of shedding is associated with poor outcomes (57). Potential therapeutic strategies to support repair of a damaged ESL, including fluid therapy prescriptions, is the focus of ongoing research.

The use of circulating biomarkers as an indicator of glycocalyx damage has limitations. These primarily include the variable methodology itself, potential for other sources of the markers since they are not unique to the glycocalyx, and upregulation of some markers with diseases such as inflammation. Further details on glycocalyx biomarkers can be found in "Resuscitative Fluid Therapy and the Endothelial Surface Layer" found elsewhere in this "Fluid Therapy in Small Animals" series.

Imaging of the ESL *in vivo*, *ex vivo*, and *in vitro* has been performed using multiple methods. These include transmission electron microscopy, (58–60) intravital microscopy, (61, 62) microparticle image velocimetry, (63) confocal laser scanning microscopy or atomic force microscopy, (10) two-photon laser scanning microscopy, (64) and videomicroscopy using handheld devices and various imaging technologies (i.e., orthogonal polarization spectroscopy, sidestream dark-field imaging incident dark-field imaging) (56). More recently, *in vivo* indirect assessments of the glycocalyx have been performed in humans and small animals using the sidestream dark-field microscopic technique in conjunction with specialized, proprietary software that measures the width of the vessel lumen available for red blood cell movement as an indirect assessment of glycocalyx thickness (also known as the perfused boundary region or PBR) (65–68). If there is damage to the ESL, RBC are able to penetrate further toward the endothelium and the PBR increases (69).

EFFECTS OF FLUID RESUSCITATION ON THE MICROCIRCULATION IN TRAUMA AND HEMORRHAGIC SHOCK

The nature of traumatic injury and hemorrhage presents significant challenges regarding how to optimize fluid therapy and volume replacement, particularly in the animal with active bleeding. In addition to loss of circulating volume, there are also aspects of progressive anemia, protein loss and coagulopathy. While administration of blood products over crystalloid or colloid is generally recommended in human medicine, (70) limited availability in veterinary medicine can result in greater use of crystalloids or consideration of synthetic colloids. Experimental hemorrhagic shock studies in rodent models suggest a benefit of balanced crystalloids, fresh frozen plasma or concentrated albumin over normal saline for restoration of the endothelial glycocalyx (71, 72). Results have not been consistent, however, Further, albumin and fresh frozen plasma appear to be more protective in most studies when compared to synthetic colloids (73). In addition to the type of fluid, volume and rate of administration are also a subject of debate; there is concern that aggressive fluid administration could serve to exacerbate ongoing hemorrhage, worsen coagulopathy, and damage the endothelial glycocalyx (74, 75). Of further consideration are the implications that fluid type and rate of administration might have on the microcirculation. As previously indicated, improving macrovascular parameters does not always correlate to restoration of microvascular perfusion.

Numerous experimental models and preclinical studies have attempted to assess the impact of various fluids on the microcirculation in patients with hemorrhagic shock. A systematic review of many of these studies, totaling 71 articles between 1990 and 2015, evaluated an assortment of fluid comparisons including blood products, hemoglobin-based oxygen carriers, crystalloids and colloids (76). Major findings of this analysis suggested that improved microcirculation was found with solutions containing hemoglobin vs. those without, those that were hyperoncotic vs. those that were not, and those that were hyperviscous vs. those that were not (76). In fitting with this, a recent study in sheep comparing hydroxyethyl starch (HES) and saline found improved hemodynamic coherence with HES, whereas saline only improved macrovascular parameters (77). However, concerns regarding the potential for acute kidney injury with synthetic colloids has served to significantly reduce their use in both human and veterinary medicine. What remains to be determined is whether use of a limited acute volume expansion carries a similar risk. In a human clinical study of patients with traumatic hemorrhagic shock, it was shown that the presence of microvascular derangement at the time of presentation that persisted after resuscitative efforts was more predictive of progression to multiple organ dysfunction syndrome than other more traditional parameters (like lactate and blood pressure) (78). This was true regardless of the type of resuscitative fluid used.

In hemorrhagic shock and trauma, there is potentially even greater interest in specifically looking at the impact of blood transfusion on restoring or maintaining microvascular perfusion. One study in human patients showed that administration of packed red blood cells helped to improve patients with microvascular parameters that were initially decreased, however there was no change or reduction in patients that started with normal values (79). Another pilot study showed improvement in microvascular parameters with red blood cell transfusion of one unit despite no change in macrovascular parameters or hemoglobin levels (80). Interestingly, these changes were negatively correlated with pre-transfusion microvascular parameters, again suggesting that the worse the microvascular impairment, the more significant the improvement. However, duration of red blood cell storage could alter the impact of red cell transfusion on microvascular perfusion. It has been demonstrated that aged red cell units may have increased levels of free hemoglobin which can serve to scavenge NO and worsen microvascular blood flow (81). Future studies evaluating the use of plasma for resuscitation from trauma are underway; initial data suggests that plasma therapy may play a beneficial role in ameliorating immunomodulatory dysfunction and trauma-induced endotheliopathy (82).

EFFECTS OF FLUID RESUSCITATION ON THE MICROCIRCULATION IN SEPSIS

Intravenous fluid therapy has been one of the cornerstones of treatment for sepsis spanning many decades. Although fluid resuscitation may improve microvascular perfusion, this effect is not predictable and likely depends in part on the timing of administration; microvascular perfusion is improved if fluids are given within 12–24 h of diagnosing sepsis but may be less effective or even deleterious when given at later stages according to one study (83). However, additional studies found that bolus fluid therapy worsened survival in people with sepsis (84, 85). Humans with abdominal sepsis displayed an increase in mean arterial blood pressure, cardiac index, and sublingual microcirculatory red blood cell velocity following a fluid challenge; however, the intestinal microcirculatory indices did not change (86). The role of fluids in the augmentation of septic endothelial dysfunction and glycocalyx damage is the focus of current investigation (87). Adverse outcomes have also been linked to fluid therapy and fluid balance, increasing the need to determine the pathogenesis of these findings (88–93). There is evidence to suggest that intravenous crystalloid and colloid fluid administration promotes endothelial glycocalyx degradation in endotoxemic sheep (94) and humans with sepsis (74, 87). Although the exact mechanism is still unknown, there are several possible etiologies: (1) acute vascular stretching along with inflammatory mediators could stimulate endothelial expression of glycocalyx-shedding matrix metalloproteinase, (95) (2) oscillatory shear stress-induced increases in cathepsin L activation (an enzyme that may be involved in post-translational activation of endothelial heparinase), (96) (3) direct activation of circulating leukocytes and trigger neutrophil-elastase glycocalyx destruction, (97–99) and (4) atrial natriuretic peptide which has been found to induce glycocalyx damage in some human studies (26, 100, 101).

The effect of the type of fluid administered may also play a role in causing glycocalyx damage with sepsis. Both clinical and preclinical data suggest that balanced crystalloids, albumin, fresh frozen plasma, and synthetic colloids may be less injurious compared to isotonic saline (102–104). It is possible that albumin preserves the glycocalyx and may be more beneficial compared to isotonic crystalloids in experimental studies, (105, 106) but results of glycocalyx evaluation following albumin therapy in septic patients are not yet available. Albumin therapy in the form of concentrated albumin or plasma products has sparked interest for its potential ability to protect the glycocalyx due to its ability to carry erythrocyte-derived sphingosine-1-phosphate to the endothelium; this may mediate glycocalyx recovery by suppressing metalloproteinase activity (107–109). It has even been suggested that individual patients should receive tailored fluid treatment plans based on admission markers of endothelial glycocalyx damage to avoid the deleterious consequences of fluid administration to patients with high risk for vascular leakage and subsequent organ dysfunction (109).

CONCLUSION

In conclusion, the hemodynamic coherence between the macro- and microcirculation is often poor in shock states such as hemorrhage or sepsis. Various diseases lead to vascular changes that may not be readily apparent with current monitoring strategies. Therefore, intravenous fluid resuscitation strategies must take into account not only microcirculatory parameters such as systemic arterial blood pressure, but also downstream measures and/or microcirculatory assessments of the patient's response to treatment. Continued research focusing on the effects or different fluid therapy prescriptions on the macro- and microcirculation/endothelial surface layer in various disease states, the goals and timing of its administration, and ultimately outcome of the patients will likely change fluid therapy in the future.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.625708/full#supplementary-material

Supplementary Video 1 | Sidestream dark-field microscopy from a healthy dog.

Supplementary Video 2 | Sidestream dark-field microscopy from a dog with hemorrhagic shock.

Supplementary Video 3 | Sidestream dark-field microscopy from a dog with septic peritonitis.

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REVIEW
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Understanding Volume Kinetics: The Role of Pharmacokinetic Modeling and Analysis in Fluid Therapy

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Fluid therapy is a rapidly evolving yet imprecise clinical practice based upon broad assumptions, species-to-species extrapolations, obsolete experimental evidence, and individual preferences. Although widely recognized as a mainstay therapy in human and veterinary medicine, fluid therapy is not always benign and can cause significant harm through fluid overload, which increases patient morbidity and mortality. As with other pharmaceutical substances, fluids exert physiological effects when introduced into the body and therefore should be considered as "drugs." In human medicine, an innovative adaptation of pharmacokinetic analysis for intravenous fluids known as volume kinetics using serial hemoglobin dilution and urine output has been developed, refined, and investigated extensively for over two decades. Intravenous fluids can now be studied like pharmaceutical drugs, leading to improved understanding of their distribution, elimination, volume effect, efficacy, and half-life (duration of effect) under various physiologic conditions, making evidence-based approaches to fluid therapy possible. This review article introduces the basic concepts of volume kinetics, its current use in human and animal research, as well as its potential and limitations as a research tool for fluid therapy research in veterinary medicine. With limited evidence to support our current fluid administration practices in veterinary medicine, a greater understanding of volume kinetics and body water physiology in veterinary species would ideally provide some evidence-based support for safer and more effective intravenous fluid prescriptions in veterinary patients.

Keywords: fluid therapy, pharmacokinetics, volume kinetics, hemoglobin dilution, urine output, distribution, elimination, half-life

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INTRODUCTION

Fluid therapy paradigms are constantly changing (1–3) due to new discoveries (4, 5) and ongoing debate on the ideal fluid choice, dose, rate, and efficacy in different patient populations (6–8). The limited and poor quality scientific literature on IV fluid therapy in veterinary medicine (9), particularly in the feline species, has given rise to empirical fluid therapy recommendations (10, 11) that are based on broad assumptions, outdated physiological principles, clinician's anecdotal experiences, or extrapolation from human clinical trials and canine experimental models. Extrapolation of data from human and canine studies are not ideal as there may be critical species variation and different fluid kinetics associated with various IV solutions. As a routine treatment

of hospitalized patients, fluid therapy has the potential to cause fluid overload which increases morbidity and mortality (12), especially in cats (13), yet we have little evidence to support our current fluid administration practices in this species (9).

The recent discovery by the "Fluid Expansion as Supportive Therapy" (FEAST) study in African children whereby standard fluid boluses significantly increased 48 h mortality (14) took the medical profession by surprise and subsequently raised many questions regarding our understanding of fluid pharmacokinetics. Since then, clinicians are more receptive to the idea that fluids should be considered "drugs" and prescribed according to the four D's (drug, dosing, duration, de-escalation) and four phases (resuscitative, optimization, stabilization, evacuation) of fluid therapy (2, 3, 15). The FEAST study is an important reminder that IV fluid therapy can exert varying physiologic effects dependent upon the context in which they are administered (16) and can be detrimental if administered inappropriately (6, 7).

For decades, research in fluid therapy was constrained by the lack of effective methods to assess important effects and outcomes. Fluid dynamics and volume expansion effects have been investigated using conventional indicator dilution techniques (17, 18), blood volume monitoring (18–20), hemoglobin dilution (21), and bioelectrical impedance analysis (22–24). In 1997, several authors (25–28) pioneered a novel and innovative pharmacokinetic (PK) model adapted for body fluid spaces that could provide descriptive data on the physiologic behavior of infused IV fluids in terms comparable to those employed in conventional PK practice (29).

For the past 20 years, Robert G. Hahn and his research group have been studying and refining the concept of volume kinetics (VK), providing a research platform to understand how administration of various IV fluids affect body fluid compartments under different physiologic conditions. Intravenous fluids can now be studied like pharmaceutical drugs, leading to improved understanding of their time-volume effects or elimination half-life on plasma and interstitial fluid compartments (30), making evidence-based approaches to fluid therapy possible. Although this concept originally served as a research model for humans (30–33), a handful of experimental studies have been performed in animals including rabbits (34), pigs (35), and sheep (36–45).

The study of VK in companion animal species is unprecedented, and there is no scientific literature currently available. In response to the call for more scientific research to build an evidence-based foundation for veterinary fluid therapy, the purpose of this review is to introduce the basic concepts of VK, its current use in human and animal research, as well as its potential and limitations as a research tool for fluid therapy research in veterinary medicine.

BASIC PHARMACOKINETIC CONCEPTS AND MODELS

Pharmacokinetics and pharmacodynamics are complex disciplines that utilize advanced mathematical principles that practitioners sometimes find challenging to comprehend. However, these two branches of pharmacology are pivotal in understanding ways to enhance efficacy and decrease harm for any exogenous substance prescribed (46), thus critical to clinical drug delivery. Pharmacokinetic analysis and simulation is the established approach to guide pharmaceutical dosing and frequency since it outlines a substance's concentration time course within the body (46). Pharmacodynamics, on the other hand, illustrate the dose-related effect of a substance in the body over time (46).

Absorption, distribution, metabolism, and excretion form the classic principles which make up the "ADME" acronym that describes PK (47). Absorption is the process where a substance travels from the site of administration to the site of measurement (46), while bioavailability refers to the degree and rate that an active substance is absorbed and present at the site of action (48). During and after the absorption phase, distribution occurs when the substance travels to and from the site of measurement (46). Volume of distribution (V_d) is a proportionality constant between measured plasma concentration and the corresponding amount of substance within the body according to the state of substance disposition, i.e., at initial time 0 ($V_{d(c)}$), under steady-state conditions ($V_{d(ss)}$), pseudo-equilibrium conditions ($V_{d(area)}$), or at any given time ($V_{d(t)}$) (49). Volume of distribution is primarily designed to determine the appropriate loading dose for rapid achievement of targeted therapeutic plasma concentration, but often interpreted indirectly to encompass the extent of substance distribution following recourse to physiological models involving plasma protein and tissue drug binding (49). Finally, elimination is the sum of metabolism and excretion (46). The term excretion, defined as the irreversible loss of chemically unchanged compound from the body, is routinely confused and used interchangeably with the term elimination, which is the irreversible loss of substance from the site of measurement (50). Most substances are eliminated by a first-order process and occurs when the amount of substance eliminated at any time is directly proportional to the amount of substance in the body, such that the fraction of elimination over time remains constant (51). Zero-order elimination, on the other hand, occurs when the amount of substance eliminated for each time interval is constant regardless of the amount of substance in the body (51).

The management of a substance by the body is an intricate process as the various components of "ADME" occur simultaneously, thereby constantly altering substance concentration in tissues and fluids (51). Application of mathematical principles simplify and help to describe these complex body processes and facilitate the anticipation of a substance's behavior within the body (51). The most fundamental model utilized in PK is the compartmental model, often designated by the number of compartments needed to depict the substance's behavior in the body, e.g., one-compartment, two-compartment, and multi-compartment models (51). The compartmental model is known as a mammillary or catenary model and is dependent on whether peripheral compartments are linked in parallel or in series to the central compartment,

respectively (52). In a mammillary compartmental model, the compartments do not represent a specific organ or fluid space, but rather a group of body tissues or fluid spaces that possess similar substance distribution patterns. Blood (plasma) and highly perfused tissues such as the heart, lungs, liver, and kidneys are often collectively regarded as the central compartment (i.e., vessel rich group), while moderately (i.e., muscle) and poorly perfused tissues (i.e., adipose tissue, cerebrospinal fluid) are considered the peripheral compartment (53).

Compartmental models are said to be deterministic because the model that best describes the PK of a substance is determined by the substance's concentrations in the blood (51). If a substance's plasma concentration-time profile best fits a one-compartment model, this denotes that the substance is dispersed instantaneously and rapidly throughout its volume of distribution (53). The plasma concentration-time profile displays a mono-exponential decline as only a single process, i.e., elimination, contributes to the decrease in plasma concentration, while the distribution phase occurs too rapidly to be charted (53, 54). If a substance's PK pattern is better fitted by a bi-exponential model, this suggests that the substance first distributes in the central compartment and then more slowly to a peripheral compartment (53). The substance distributes back and forth between these two compartments and leaves the body from the central compartment (53). This leads to a plasma-concentration time profile with a bi-exponential decline characterized by two distinct phases: (1) the distribution phase which is the initial steep decline in plasma concentration, and (2) the elimination phase which is the subsequent slower decline in plasma concentration sustained by redistribution of substance from the peripheral compartment (54).

The merit of any model depends on how well it mimics the substance's concentration in the body. Typically, the simplest model that sufficiently predicts changes in substance concentration over time is selected (51). A concentration-time curve can be plotted following serial substance plasma concentration measurement and logarithmically transformed to demonstrate a mono-phasic or bi-phasic time profile (53). Subsequently, any unknown concentrations can be predicted and simulated (51). In PK studies, appropriate doses and dosing intervals are determined using computer simulation after repeated experimental measurements of plasma drug concentration are conducted and compared with theoretical computer-generated concentration-time data using non-linear least squares regression (55).

The conventional way to present PK output is to analyze each subject individually and report the mean parameter values for a group as the "typical parameter values" for that cohort. An alternative approach is to analyze all subjects in one single analysis while keeping track of the between-individual variability. The widespread adoption of such population modeling in human pharmacology, also known as non-linear mixed effects (NLME) modeling, provides a framework to characterize sources of variability in drug disposition and response using statistical models that account for between- and within- individual and experimental variation (56–58). Identification and quantification of primary determinants of between-individual variability allow for improved and tailored use of therapeutic drugs, including individualization of dosage regimes and optimization of dosing schedules (58). Population models are referred to as NLME models due to the inclusion of fixed (i.e., constant within the population) and random (i.e., unexplained and varied within the population) effects parameters that possess a non-linear relationship (58). Between-individual variability can be explained by population characteristics or covariates (e.g., species, breed, age, sex, body weight, disease status, etc.) that are included additively or proportionally to the vector of population parameters or fixed effects (58). Random effect parameters represent variability in PK parameter estimates secondary to between- and within- individual variability (58). NLME modeling can be used for analysis of sparse data collected in scenarios where frequent blood sampling is challenging, dense data collected from a small study population, separate plasma and tissue PK studies, and meta-analysis of published data across disparate study designs (57, 58). These attractive advantages of NLME are recognized to be of value with potential widespread applications in veterinary pharmacology (57, 58).

BASIC CONCEPTS OF VOLUME KINETICS

Volume kinetics (VK) is an adaptation of PK theory allowing insights into the effects of IV fluid on theoretical body fluid compartments (25, 30–33, 55). This approach describes changes in plasma volume (PV) during and after IV fluid infusion over time (27). Volume kinetics can also be used to explore the distribution-elimination pattern of IV fluids under various physiological conditions and simulate any infusion fluid choice or rate to achieve desirable PV expansion (32, 33). Visual inspection of the plasma dilution-time curves provides imperative information on the magnitude and time course of PV expansion following actual IV fluid infusion (26). Meanwhile, computer simulation of plasma dilution-time profiles for any hypothetical fluid infusion using the generated kinetic parameter estimates allows insight into how IV fluid therapy should be planned. **Figure 1** illustrates an example of information attainable from visual inspection of plasma dilution-time curves (59).

When "ADME" concepts are put into the context of IV fluid administration, the absorption is instantaneous with a 100% bioavailability, metabolism is irrelevant, therefore leaving only distribution and elimination to be considered. The central concepts of both PK and VK analyses are therefore dependent upon the volume of distribution and clearance of an administered substance (31). As in PK, a theoretical mathematical model that corresponds reasonably well to the physiological dynamics of IV fluid is constructed (32, 33). The basic mathematical models developed in VK are known as the volume of fluid space (VOFS) kinetic models. These are designated by the number of fluid spaces necessary that mimic the kinetics of IV fluid within the body akin to traditional PK analysis, e.g., one-volume fluid space (1-VOFS), two-volume fluid space (2-VOFS) kinetic models, etc. (25). Both PK and VK models are admittedly challenging to conceptualize, given that they are mathematical derivatives

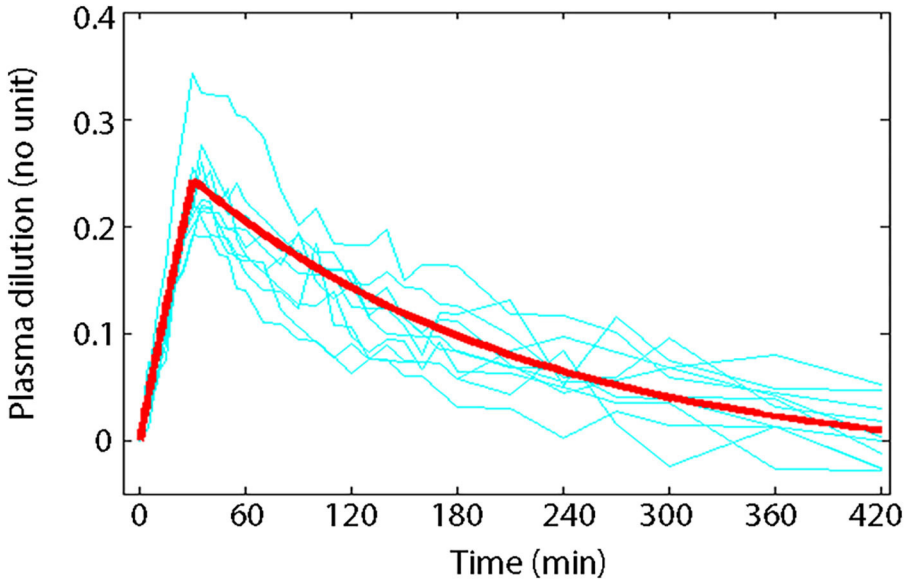

FIGURE 1 | Principle of volume kinetics. Measured plasma dilution-time curves of individual subjects (thin lines) and VK modeled plasma dilution-time curve (thick line) during and after a 30 min IV infusion of 10 mL/kg of 6% HES 130/0.4/9:1 (Voluven®) in 10 healthy male volunteers with mean body weight of 79 kg (59). Serial Hb measurements were obtained throughout the study; hemodilution was corrected to baseline HCT to express plasma dilution. Dividing the total infused volume (790 mL) by the plasma dilution extrapolated to 0.27 at time 0 yielded a *V* of 2.9 L, which approximates the expected size of PV in healthy humans, implying that Voluven® only distributes in the plasma space in health. Plotting the plasma dilution-time curve on a logarithmic paper suggested that Voluven® intravascular half-life is 120 min in healthy humans.

that do not possess precise tangible anatomical or physiological connections (31).

Unlike pharmaceuticals, water is the main component of both infusion fluids and plasma (30, 31), therefore plasma concentration of IV fluids has to be expressed differently. Blood hemoglobin (Hb) has become an attractive endogenous dilution indicator for blood volume (BV) estimation (21) and correlates inversely with blood water concentration (26). Therefore, serial measurement of acute changes in Hb concentration, which is confined to the intravascular space, can be used as a surrogate marker for IV fluid concentration in VK (32, 55). Serum albumin has been explored as a potential endogenous dilution indicator for VK analysis, however possible loss of albumin into the interstitium negated its use (26). The main assumption of VK modeling and analysis is that Hb remains constant and distributes homogenously with the infused fluid in the circulation, such that serial Hb changes are reflective of IV fluid kinetics.

Volume of distribution (V_d) in conventional PK analysis is not easily applied to fluid therapy. Unlike conventional PK, where V_d is assumed constant as the volume of administered drug is often negligible, the volume of distribution of IV fluid (denoted by the symbol v) continually changes as a direct consequence of IV fluid administration. Therefore, the baseline output parameter, volume of expandable body fluid space (V), representing the volume of distribution of initial fluid infusion is estimated instead in VK (34). Depending on the kinetic model used, V can be further categorized as the volume of expandable central body fluid space (V_c) and the volume of expandable peripheral body fluid space (V_p). V can only be estimated from plasma dilution measurement and represents the functional fluid space actually expanded by IV fluid (26). Therefore, V may not always equate to the size of body fluid spaces estimated by external indicator-dilution techniques that disperse into the extracellular fluid spaces of minimally expandable structures such as bone, cartilage, dense connective tissue, and organs confined by tight fibrous capsules (34).

Aside from the above interpretation differences, the mathematical solutions and data analysis are analogous to PK compartmental modeling. Volume kinetic models are based on the assumption that plasma dilution follows a mono-exponential (1-VOFS kinetic model) or bi-exponential (2-VOFS kinetic model) curve. The dilution-time profiles, sometimes augmented by urinary excretion (60), are entered into commercial computer software and fitted to the differential equations describing the fluid shifts in these kinetic models (25). Non-linear least-squares regression is used to generate the best kinetic parameter estimates from the differential equations relevant to each kinetic model (25). Subsequently, analytical or matrix solutions to the differential equations are solved to compute V as well as the kinetic constants governing fluid distribution (25). Similar to PK modeling, the kinetic model with the simplest solution should be chosen (31) and statistical tests can be applied to select the best fitted model for presentation (61, 62). Agreement between model-predicted renal clearance (Cl_R) and actual urine output measurement may also assist in final model selection (32).

Following that, computer simulation of dilution-time profiles for hypothetical fluid infusion can be accomplished

by inputting the mean parameter estimates obtained from non-linear least-squares regression into the differential equation solution describing the kinetic model (25). Various commercial mathematical programs such as MATLAB® (MathWorks® Inc, Natick, MA, USA) (63, 64) or specialized PK modeling and simulation software such as Monolix (Lixoft, Antony, France), Phoenix WinNonlin® or Phoenix® NLME™ (Certara USA, Inc., Princeton, NJ, USA) (65) can be utilized for this purpose.

HISTORY AND EVOLUTION OF VOLUME KINETIC MODELING

The original VK models were first developed in 1997 based on the concept of clearance and plasma dilution (25–27). The most commonly encountered problems with earlier VK analyses included overestimation and poor precision when estimating the size of the peripheral fluid space (V_p), which became an issue with slow fluid elimination (25, 26, 66, 67). Over the years, efforts to refine and improve the robustness of these models were made, including the incorporation of urine output as an input variable to VK analysis (60).

Parameter estimates from earlier VK studies are challenging to interpret and compare because they are derived using different kinetic methodologies. This eventually led to a major modification to the VK approach in 2006 which allows for a single comprehensive model solution for isotonic crystalloid solutions (67). In this modified "micro-constant" analysis, the fractional plasma dilution is substituted with absolute volume expansion, flow rate (unit: mL/min) parameters are substituted with rate parameters (unit: /min), and the existence of V_p is acknowledged but its size is not routinely estimated (67). Despite these changes, this modified model still describes the same functional system as the antecedent models (27, 60, 66, 68) and is able to address bi-directional fluid flux, i.e., outflow when plasma dilution is high, inflow when distributed fluid exerts greater force than V_c (67). Since then, progressively sophisticated extensions have been explored to address specific clinical research questions including three-volume kinetic modeling which accounts for hypertonic osmotic fluid shifts (37, 68), volume turnover kinetics to predict fluid dynamics following hemorrhage and fluid resuscitation (41), and population kinetic modeling that enables the inclusion of various physiological covariates (69–74).

Over the past 10 years, VK has gradually moved away from the clearance model to the micro-constant model where clearance variables (Cl, Cl_d, Cl_0) are substituted by rate constants (k_{10}, k_{12}, k_{21}, k_0) and fractional plasma dilution ($\frac{(v_c - V_c)}{V_c}$) is replaced by absolute volume expansion ($v_c - V_c$) (32, 33) in the kinetic equations. The clearance and micro-constant models are essentially one and the same, except that the former deals with fractional plasma dilution and flow rate (unit: mL/min), while the latter deals with absolute volume expansion and rate (unit: /min). The same Hb-derived plasma dilution is still used to indicate the volume expansion of V_c resulting from IV infusions (59). The micro-constant model is preferred over the clearance model as fluid volumes within the different body fluid spaces are now directly apparent and unequal fluid distribution across V_c and V_p compartments can be further investigated (30, 33).

With the evolution of VK models over time, many parameters have been represented differently, and so it is important to review the literature with an eye to this evolution to not be confused by the changes in symbols and parameters. This is further complicated by the use of proprietary symbols and expressions between PK computer software and PK studies (75). This has created a great degree of confusion and ambiguity, making PK and VK difficult to understand. Consistency in the use of symbols, units, and nomenclature would hopefully clarify the precise meaning of the term or concept as defined, curtail erroneous interpretation, and allow meaningful comparison between studies.

The following symbols and abbreviations are deduced to be equivalent dependent on whether a clearance model or a micro-constant model is presented: $V_1 = V_c$, $V_2 = V_t = V_p$, $v_1 = v_c$, $v_2 = v_t = v_p$, $k_i = R_0$, $k_b = Cl_0 = k_0$, $k_r = Cl \cong k_{10}$, and $k_t = Cl_d \cong k_{12}$ and k_{21} (25, 32, 59, 67). To improve uniformity and clarity, the parameters, symbols, and abbreviations analogous to those used in PK (75, 76) should be used. Comparison of conventional PK and analogous VK parameters are summarized in **Table 1**.

TWO-VOLUME FLUID SPACE KINETIC MODEL

Most IV fluids can be modeled using a 2-VOFS kinetic model (33, 55), also referred to as the bi-exponential model. The 2-VOFS kinetic model has been reported to best describe the effects of fluid therapy in human patients receiving crystalloid infusions during surgery, general anesthesia, dehydration, and hypovolemia (32), but does not always seem to describe the situation in healthy human volunteers (26, 27, 68) likely due to the rapid elimination of crystalloids in healthy awake states.

The 2-VOFS model, as illustrated by **Figure 2**, suggests that IV fluid administered at a certain rate (R_0) would expand the volume of a central body fluid space (V_c) to a larger volume (v_c) (32). As transcapillary hydrostatic and colloid osmotic pressure changes, the fractional plasma dilution ($\frac{v_c - V_c}{V_c}$) (26, 32) or absolute volume expansion ($v_c - V_c$) (67, 77, 78) indicate distribution of fluid to a peripheral body fluid space (V_p) which in turn expands to a greater volume (v_p). These central and peripheral body fluid spaces attempt to retain their respective initial volumes to maintain homeostasis (26, 32). The net rate of fluid flux between the central and peripheral body fluid spaces is governed by the volume expansion difference between V_c and V_p multiplied by the distribution clearance (Cl_d) in the clearance model (32, 79), or the intercompartmental rate constants (k_{12}, k_{21}) in the micro-constant model (67, 77, 78). In the micro-constant model, intercompartmental rate constants can be further categorized into central to peripheral intercompartmental rate constant (k_{12}) and peripheral to central intercompartmental rate constant (k_{21}) akin to PK analysis (67, 77).

Fluid elimination occurs from the central body fluid space via two mechanisms: (a) baseline water loss which is accounted

TABLE 1 | Comparison of conventional pharmacokinetic and analogous volume kinetic parameters.

Parameters	Pharmacokinetics	Volume kinetics[a]
Modeled entity (unit)	Mass, X (mg)	Volume expansion, $(v - V)$ (mL)
Quantity in body (unit)	Amount, $A = C_p \times V_d$ (mg)	Volume expansion, $(v - V) = \frac{Hb/Hb_{(t)} - 1}{1 - HCT} \times V$ (mL)
Primary input variable (unit)	Concentration, $C_p = \frac{A}{V_d}$ (mg/mL)	Plasma dilution, $\frac{(v-V)}{V} = \frac{Hb/Hb_{(t)} - 1}{1 - HCT}$ (dimensionless)
Key parameters of interest (unit)	Volume of distribution, $V_d = \frac{A}{C_p}$ (mL) Total clearance, CL_T (mL/min)	Volume of body fluid space, V or V_c (mL) Clearance model: Cl, Cl_d (mL/min) Micro-constant model: k_{10}, k_{12}, k_{21} (/min)
Intravenous infusion rate (unit)	R_0 (mg/min)	R_0 (mL/min)
Zero-order elimination (unit)	Fixed amount of substance eliminated per unit time: e.g., Ethanol	Clearance model: Basal fluid losses, Cl_0 (mL/min) Micro-constant model: Basal fluid losses, k_0 (mL/min)
First-order elimination (unit)	Constant fraction of substance eliminated per unit time: e.g., Most drugs k_{10} (/min)	Clearance model: Cl (mL/min) Micro-constant model: k_{10} (/min)
Intercompartmental rate constants (unit)	k_{12}, k_{21} (/min)	Clearance model: Distribution clearance, Cl_d (mL/min) Micro-constant model: k_{12}, k_{21} (/min)
Change in quantity per time (unit)	$\frac{dA}{dt} = R_0 - k_{10} \times C_{p(t)}$ (mg/min)	Clearance model: $\frac{dv}{dt} = R_0 - Cl \times \frac{(v_{(t)} - V)}{V}$ (mL/min) Micro-constant model: $\frac{dv}{dt} = R_0 - k_{10} \times (v_{(t)} - V)$ (mL/min)
Rate of elimination (unit)	$R_{el} = CL_T \times C_{p(t)}$ (mg/min)	Clearance model: $R_{el} = Cl \times \frac{(v_{(t)} - V)}{V}$ (mL/min) Micro-constant model: $R_{el} = k_{10} \times (v_{(t)} - V)$ (mL/min)

(Continued)

TABLE 1 | Continued

Parameters	Pharmacokinetics	Volume kinetics[a]
Renal clearance (unit)	$CL_R = \frac{\text{Amount in urine}}{AUC \text{ for plasma conc.}}$ (mL/min)	Clearance model, $Cl \cong Cl_R$: $Cl_R = \frac{\sum \text{urine volume}}{AUC \text{ for plasma dilution}}$ (mL/min) Micro-constant model: $Cl_R = \frac{\sum \text{urine volume}}{AUC \text{ for volume expansion}}$ (mL/min)
Elimination half-life (unit)	$t_{1/2} = \frac{0.693 \times V_d}{CL_T}$ (min)	Clearance model: $t_{1/2} = \frac{0.693 \times V}{Cl_R}$ (min) Micro-constant model: $t_{1/2} = \frac{0.693}{k_{10}}$ (min)

[a]*Expressions for 1-VOFS kinetic model parameters are presented. Expressions for 2-VOFS kinetic model parameters are similar by substituting V and v with V_c and v_c, respectively. X, mass; A, amount; C_p, plasma drug concentration; V_d, volume of distribution; v, volume of expanded body fluid space; V, volume of expandable body fluid space; Hb, hemoglobin; $Hb_{(t)}$, hemoglobin at any time t; HCT, hematocrit; V_c, volume of expandable central body fluid space; CL_T, total clearance; Cl, first-order clearance; k_{10}, first-order elimination rate constant; Cl_d, distribution clearance; k_{12}, central to peripheral intercompartmental rate constant; k_{21}, peripheral to central intercompartmental rate constant; R_0, intravenous infusion rate; Cl_0 or k_0, zero-order basal fluid losses; R_{el}, rate of elimination; $v_{(t)}$, volume of expanded body fluid space at any time t; $C_{p(t)}$, plasma drug concentration at any time t; ≅, approximately equal to; ∑, sum of; CL_R or Cl_R, renal clearance; AUC, area under concentration-time curve; $t_{1/2}$, half-life (31–33, 75, 76).*

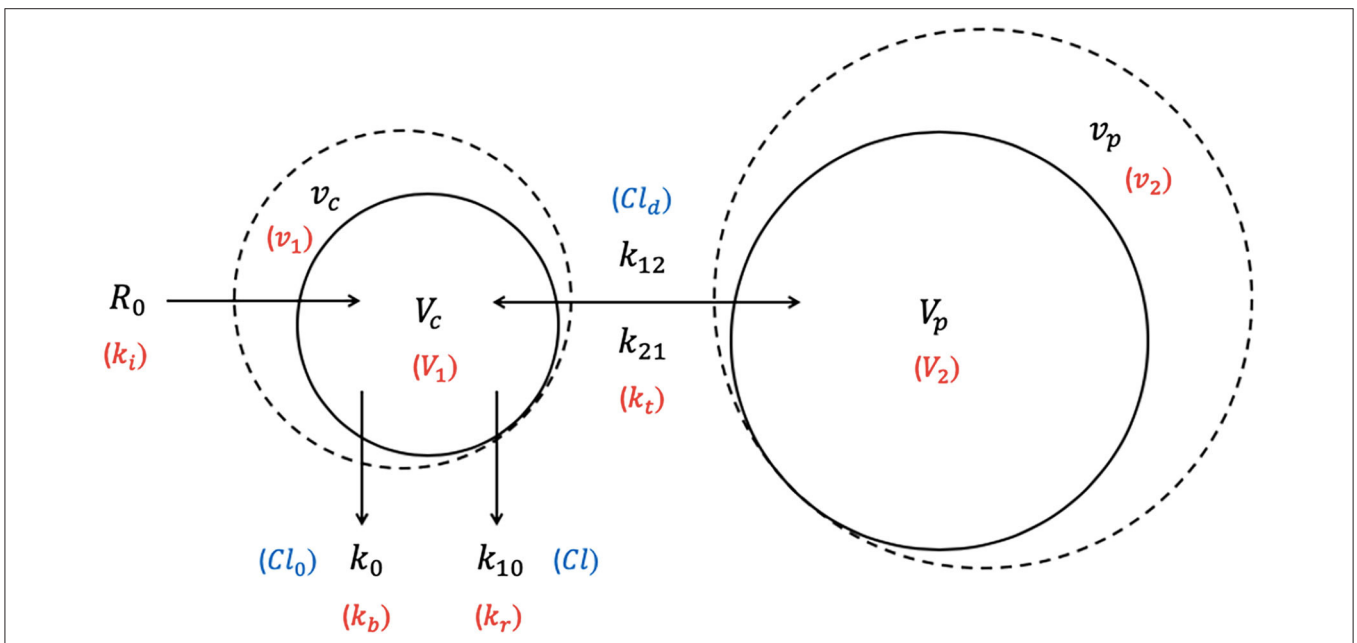

FIGURE 2 | Two-volume fluid space (2-VOFS) kinetic model. Adapted from previous VK work (25, 26, 32, 67, 77–79). The symbols in black represent the current micro-constant model (67, 77, 78), whereas the symbols within red parentheses represent the original model (25, 26) and the symbols within blue parentheses represent the clearance model (32, 79).

for by zero-order elimination (Cl_0 or k_b) often pre-set between 0.3 and 0.5 mL/min in humans (66, 68, 80), and (b) dilution-dependent, primarily renal excretion governed by first-order elimination (Cl or k_{10}) (32). The rate of elimination is given by the product of fractional plasma dilution ($\frac{v_c - V_c}{V_c}$) (26, 32) or absolute volume expansion ($v_c - V_c$) (67, 77, 78), and the first-order elimination clearance (Cl) or elimination rate constant (k_{10}) (32).

The unknown parameters in the 2-VOFS kinetic model that are estimated by non-linear least-squares regression are V_c, Cl_d (or k_{12} and k_{21}), and Cl (or k_{10}) (31). If urine output is measured, k_0 can even be estimated and includes all other body fluid not allocated by the VK model along with the basal fluid loss (32, 60). The first-order elimination (Cl or k_{10}) is then set to a fixed value determined by the total urinary excretion obtained. In this scenario, Cl is analogous to the renal clearance which

is calculated by dividing the urine output by the integral of the plasma dilution-time curve, also known as the area under concentration-time curve (*AUC*), following the assumption that half of the Cl_0 or k_0 due to insensible fluid losses appears as urine (60). The following differential equations describe the clearance model for the 2-VOFS kinetic model (30):

$$\frac{dv_c}{dt} = R_0 - Cl_0 - Cl\frac{(v_c - V_c)}{V_c} - Cl_d\left[\frac{(v_c - V_c)}{V_c} - \frac{(v_p - V_p)}{V_p}\right] \quad (1)$$

$$\frac{dv_p}{dt} = Cl_d\left[\frac{(v_c - V_c)}{V_c} - \frac{(v_p - V_p)}{V_p}\right] \quad (2)$$

The differential equations describing the micro-constant model for the 2-VOFS kinetic model are as follows (30):

$$\frac{dv_c}{dt} = R_0 - k_0 - k_{10}(v_c - V_c) - k_{12}(v_c - V_c) + k_{21}(v_p - V_p) \quad (3)$$

$$\frac{dv_p}{dt} = k_{12}(v_c - V_c) - k_{21}(v_p - V_p) \quad (4)$$

By comparing Equation (1) for the clearance model with Equation (3) for the micro-constant model, net Cl_d is obtained as the product of $V_c \times k_{12}$ and $V_p \times k_{21}$ (30). Similarly, Cl is the product of $V_c \times k_{10}$ (30).

ONE-VOLUME FLUID SPACE KINETIC MODEL

Intravenous fluid plasma dilution-time profiles may not always display the bi-exponential form of a 2-VOFS kinetic model and sometimes statistically fit the 1-VOFS kinetic model better (32). A common scenario where this occurs is when crystalloids are eliminated rapidly from the body (27, 68), leading to an increased $Cl : Cl_d$ (or $k_{10} : k_{12}$ and k_{21}) ratio. This reduces the time for full V_p expansion prior to elimination, therefore V_c and the partially expanded V_p fuse into a moderate size single body fluid space, allowing 1-VOFS kinetic model to sufficiently describe these dilution-time profiles (32). In addition, colloidal solutions with high molecular weight polymers that do not distribute extensively into the extravascular tissues should theoretically be described by the 1-VOFS kinetic model (31).

The 1-VOFS kinetic model, also known as the mono-exponential model, is illustrated by **Figure 3**. As the name suggests, IV fluid administered at a given rate (R_0) is thought to expand the volume of a single body fluid space (V) to a larger volume (v) (32). Elimination of fluid still occurs via basal fluid losses (Cl_0 or k_b) and a dilution-dependent, primary renal excretion governed by a first-order elimination (Cl or k_{10}) (32). The unknown parameters in the 1-VOFS kinetic model that are estimated by non-linear least-squares regression include V and Cl (or k_{10}) (31). The fractional plasma dilution ($\frac{(v - V)}{V}$) in the clearance model or absolute volume expansion

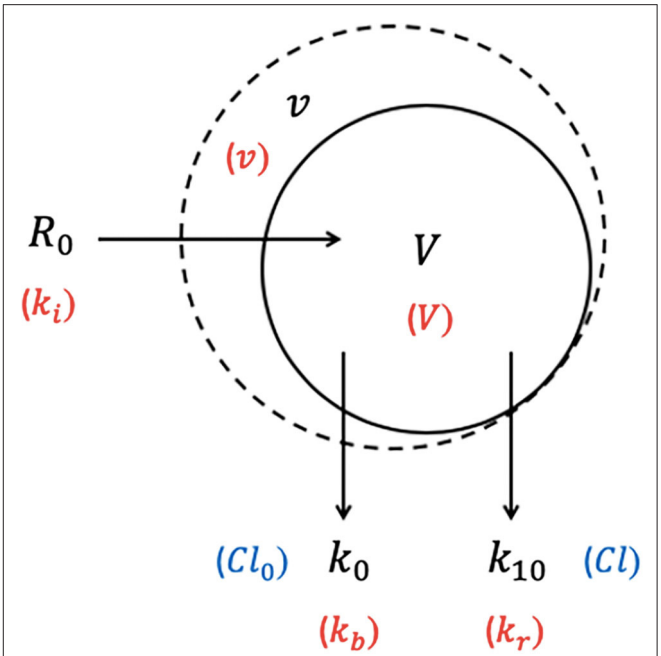

FIGURE 3 | One-volume fluid space (1-VOFS) kinetic model. Adapted from previous VK work (25, 26, 32, 67, 77–79). The symbols in black represent the current micro-constant model (67, 77, 78), whereas the symbols within red parentheses represent the original model (25, 26) and the symbols within blue parentheses represent the clearance model (32, 79).

$(v - V)$ in the micro-constant model, is obtained from plasma dilution computed from serial Hb concentration. Similar to the 2-VOFS kinetic model, Cl_0 and Cl can be estimated through VK modeling or calculated if urine output is available. The following differential equation describes the clearance model for the 1-VOFS kinetic model (32, 79):

$$\frac{dv}{dt} = R_0 - Cl_0 - Cl\frac{(v - V)}{V} \quad (5)$$

In comparison, the differential equation that describes the micro-constant model for the 1-VOFS kinetic model is as below (67, 77, 78):

$$\frac{dv}{dt} = R_0 - k_0 - k_{10}(v - V) \quad (6)$$

MASS BALANCE PRINCIPLES

The volumes of individual body fluid compartments are conventionally estimated using external indicator-dilution techniques. Some examples include but are not limited to, deuterium oxide (81) or radioactive tritium oxide (82) for total body water determination; bromide (83, 84) for extracellular fluid volume determination; and radio-iodinated serum albumin (18), Evans Blue dye (18, 36), or indocyanine green dye (17, 18, 38) for plasma volume determination. Based on the law of mass conservation, indicator-dilution techniques fulfill the mass balance principle at steady-state, whereby the total indicator

mass following distribution in the fluid compartment will remain the same as the total mass injected into the compartment (80, 85). Hence, the volume of a body fluid compartment can be estimated provided that the indicator's concentration following homogenous mixing can be accurately determined (84).

Although exogenous indicator-dilution techniques are considered the conventional "gold standard" method for volume determination (17, 86), they can result in hypersensitivity reactions and potential errors as a result of indicator extravasation, plasma turbidity, Hb contamination, or controversial back-extrapolation methods (18, 87–90). Radioactive isotopes are cumbersome to use and there is a significant time delay for exogenous indicators to equilibrate to a steady-state distribution (80, 84). This precludes the ability to distinguish between the distribution and elimination phases (34, 67) and does not permit analysis of acute dynamic fluid shifts (36).

In 1987, an endogenous indicator-dilution technique using blood Hb concentration was introduced as an accurate method for estimation of BV changes following validation with the radio-iodinated serum albumin technique (21). Endogenous Hb is confined solely within the plasma space, not associated with any time-delay for steady-state equilibrium, much easier to use, and widely measurable in routine clinical laboratories (21, 67). Therefore, serial measurement of Hb concentrations following IV fluid administration can be used to quantify plasma dilution in the blood and represent acute dynamic fluid shifts within the body (21). The mass balance technique using serial Hb dilution requires the assumption that total body Hb remains constant and homogenously distributed within the circulation at all times, except during sampling losses or hemorrhage to which correction for Hb losses can be made (21, 38).

HEMOGLOBIN-DERIVED PLASMA DILUTION

Plasma and Hb are the main components of the central body fluid space, and the change in V or V_c is directly proportional to plasma dilution (26). Therefore, serial measurement of Hb concentrations following IV fluid administration can be used to quantify plasma dilution in the blood. Hemoglobin dilution must be converted to the corresponding plasma dilution considering that extracellular fluid, and not red blood cells (RBC), are expanded by the infused fluid. Moreover, PV is the actual entity that distributes across body fluid spaces and from which water is ultimately eliminated from the body. Plasma dilution, which equals the dilution of V or V_c, is used to quantitate fluid volume load. As such, the concentration of IV fluid, or volume expansion, is expressed in terms of Hb-derived plasma dilution as a function of time (32), given by the reference Equation (7). This reference equation can be applied directly into the non-linear least square regression curve-fitting procedure if blood sampling and hemorrhage are negligible.

$$Plasma\ dilution,\ \frac{v_{(t)} - V}{V} = \frac{\frac{Hb_{(0)} - Hb_{(t)}}{Hb_{(t)}}}{1 - HCT} = \frac{\frac{Hb_{(0)}}{Hb_{(t)}} - 1}{1 - HCT} \quad (7)$$

Simultaneously measured RBCs are diluted similarly as Hb during IV fluid loading but quantified using a different technique by the automated hematology analyzer. Therefore, if available, RBC count and RBC mass could also be included in the curve-fitting procedure to improve precision and accuracy (32), although the author's (RGH) experience with this adaptation yielded negligible effect. The same calculations using the reference Equation (7) are performed for RBC count and RBC mass over time, and the mean value for Hb-derived plasma dilution and RBC-derived plasma dilution can be used as the overall plasma dilution (91). Calculated hematocrit value obtained from automated hematology analyzers is preferred over packed cell volume for plasma dilution determination as the latter frequently overestimates true RBC fraction due to incomplete microhematocrit centrifugation compaction (80).

CORRECTIONS FOR HEMOGLOBIN LOSS

Serial blood sampling can result in sufficient loss of Hb creating a "false" dilution that is unrelated to IV fluid therapy. Therefore, blood loss and sampled volume should be corrected prior to the curve-fitting procedure. The calculations to correct for Hb loss and alteration in erythrocyte size consider the PV expansion instead of plasma dilution. To account for sampling loss, change in BV is calculated by estimating the total Hb mass in the circulation from which blood loss is subtracted (21). An assumption of initial BV has to be preset to time 0 (31). The total baseline Hb mass ($MHb_{(0)}$) is first obtained, then the total Hb mass corrected for sampling at any time (t), followed by the expanded BV corrected for sampling at any time (t) (32):

$$MHb_{(0)} = BV_{(0)} \times Hb_{(0)} \quad (8)$$

$$MHb_{(t)corr.} = MHb_{(0)} - \left[\left(sampled + bled\right)\ volume \times Hb_{(t)}\right] \quad (9)$$

$$BV_{(t)corr.} = \frac{MHb_{(t)corr.}}{Hb_{(t)}} \quad (10)$$

Changes in BV at any time (t) can be provided by Equation (11), and the BV expression can be easily transformed to PV using Equation (12):

$$\Delta BV = BV_{(t)corr.} - BV_{(0)} \quad (11)$$

$$PV = BV \times (1 - HCT) \quad (12)$$

$$PV_{(t)} = BV_{(t)} \times \left[1 - HCT \times \frac{Hb_{(t)}}{Hb_{(0)}}\right] \quad (13)$$

Corrected plasma dilution,

$$\frac{v_{(t)} - V}{V} = \frac{PV_{(t)} - PV}{PV} \quad (14)$$

The relationship between baseline Hb ($Hb_{(0)}$) and diluted Hb at any time (t) is written as $\frac{Hb_{(0)}}{Hb_{(t)}}$ in the reference Equation (7), whereas the inverse relationship is used in Equations (13, 14) (32). The lower Hb concentration must be placed as the denominator of the ratio in the reference Equation (7) to arrive at a correct proportion between changes in Hb and water volume.

The degree of error introduced by the wide range of initial BV has been shown to be forgiving (66), however the error related to frequent blood sampling and the use of successive Hb ratio for volume estimation should not be ignored as the volume-estimation errors can increase exponentially (92). Given the importance of an accurate baseline value, averaging duplicate and triplicate Hb measurements on the initial blood sample is strongly recommended, and the percent coefficient of variation for the entire sampling and analysis should be determined (92). Duplicate Hb measurements for subsequent blood samples throughout the studies have been attempted by the author (RGH) with marginal improvement to VK analysis.

CORRECTIONS FOR ALTERNATION IN MEAN CORPUSCULAR VOLUME AND OSMOTIC FLUID SHIFT

When investigating IV fluids that alter plasma osmolality, for example hypertonic saline (HS) or glucose infusions, a correction for changes in mean corpuscular volume should also be considered. Mean corpuscular volume can be altered in humans following infusion of HS because of osmotically induced decreases in intracellular water, this has also been reported in dogs and cats (93). Changes in mean corpuscular volume can be considered by the addition of a term for the relationship between the baseline ($MCV_{(0)}$) and at any time (t) into Equation (13) above:

$$PV_{(t)} = BV_{(t)} \times \left[1 - HCT \times \frac{Hb_{(t)}}{Hb_{(0)}} \times \frac{MCV_{(t)}}{MCV_{(0)}}\right] \quad (15)$$

If HS or glucose solutions are infused, an osmotic fluid shift theoretically occurs across the cell membrane and water moves from the intracellular fluid space (∼40% of BW) to the extracellular fluid space (∼20% of BW) (80). Using species-specific baseline serum osmolality ($Osm_{(0)}$), which is ∼295 mOsm/kg for humans (32), ∼317 mOsm/kg for cats (94), and ∼302 mOsm/kg for dogs (95), the translocated volume (f_t) can be obtained from Equation (16) (37, 68):

$$\frac{BW \times 20\% \times Osm_{(0)} + \text{infused osmoles}}{BW \times 20\% + f_t + \text{infused volume}} = \frac{BW \times 40\% \times Osm_{(0)}}{BW \times 40\% - f_t} \quad (16)$$

The osmotic force diminishes progressively with subsequent amount of infused fluid; therefore, f_t should be entered as a linear function in the analysis process such that f_t at each point in time is governed by the total amount of infused fluid (32).

VOLUME KINETIC MODELS IN PHYSIOLOGICAL CONTEXTS

Recall that PK compartment models and VK kinetic models are mathematical concepts that describe body spaces which a substance or fluid appears to occupy, but may not correspond to an actual anatomical space or physiological volume (31, 54). In PK analysis, V_d is theoretical and does not equate to a real volume (53, 54). A substance could have a large V_d that substantially exceeds the total body volume (54), implying that it is highly distributed in tissues (53). The smallest V_d is the PV (51) which suggests that the substance is poorly distributed and confined to the plasma (53). Similarly, this concept applies to V and V_c which substitute V_d in VK analysis.

In healthy human VK studies, the size of V_c for crystalloids using a 2-VOFS kinetic model has been reported as 3–4 L (4–6% of BW) (26, 31, 60, 68), which is similar to the expected (80) and measured human PV (69). However, when a 1-VOFS kinetic model is used, the size of V is usually twice the size of PV (59, 60, 68) as it combines both the plasma volume and approximately half of the interstitial fluid volume. As is expected for colloids, the size of V of a 1-VOFS kinetic model was found to be analogous to the PV (59).

The size of V_p in healthy adult humans was discovered to be 6–8 L (8–11% of BW) (26, 68, 96), which is smaller than the expected size of the interstitial fluid space (11 L or 15% of BW) (80). The V_p encompasses about 66.6% of the interstitial fluid space since bones, cartilage, dense connective tissues, and organs with a tight fibrous capsule are either not expandable or minimally expandable by fluid (26, 34, 96). Unlike the conventional exogenous indicator-dilution techniques, VK only highlights expandable body fluid spaces (26). Some interstitial tissues have increased compliance for volume expansion while others require very elevated fluid pressure before expansion can occur (97, 98). The V_p was discovered to be larger when massive fluid infusions beyond what is routinely safe in clinical practice were administered to sheep (39). The precision of V_p is often lower than V_c (26, 32, 60) but is less crucial since the size of V_p does not contribute significantly to interpretable knowledge (67). So far, estimates of V_p that are significantly smaller than V_c have not been reported (67).

In healthy humans, there should be no restriction on fluid movement into the peripheral body fluid space or return to the central body fluid space. Distribution clearance (Cl_d) or the intercompartmental rate constants (k_{12}, k_{21}) can be appointed the same value for bi-directional flow based on the assumption that fluid is equally prone to flow in either direction (32). Alternatively, uneven distribution can be analyzed using the micro-constant model by splitting the intercompartmental rate constants into k_{12} and k_{21}, which could serve to quantify the accumulation of peripheral edema (30, 36, 38). Fluid exchange is considered normal with k_{12} that is twice as high as k_{21} (33, 71, 77).

According to the model, the parameter Cl (or k_{10}) that is estimated by non-linear least square regression should approximate the renal clearance (Cl_R), since the ultimate destiny of IV fluid is elimination via the kidneys (31). It is, however, important to remember that parameter estimates generated from VK modeling are not absolute measurements of physiologic body fluid variables, but rather represent estimates of abstract concepts which provide insights into the body's handling of IV fluid (31). The first-order elimination rate constant has been found to correlate well with urine output in human volunteers receiving

TABLE 2 | Clinical implications of volume kinetics in healthy and sick animals.

	Clinical implications
Healthy animals	1. The distribution and elimination of isotonic crystalloid fluid bolus in sheep are markedly different under awake and anesthesized states (36, 38). a. Isotonic crystalloid solution is rapidly eliminated from the intravascular space via urinary excretion in awake sheep (36, 38). b. Isoflurane anesthesia significantly decreases urinary excretion (fluid elimination), leading to peripheral fluid distribution and accumulation (36, 38). 2. Large, rapid isotonic crystalloid fluid boluses exceeding renal excretory capacity contribute to peripheral fluid accumulation in sheep (39). 3. Vasoactive agents alter the distribution and elimination of isotonic crystalloid fluid in healthy awake sheep (43, 45). a. α_1-adrenergic stimulation reduces PV expansion by increasing fluid elimination (urinary excretion) and peripheral fluid distribution (43, 45). b. β_1-adrenergic stimulation reduces fluid elimination and peripheral fluid distribution, thereby improving hemodynamics through more effective PV expansion (43, 45). 4. Mannitol infusion has lower PV expansion effects and contributes to peripheral fluid accumulation in pigs due to higher fluid elimination (osmotic diuresis) and fluid distribution down the osmotic gradient (natriuresis-induced and dilutional hyponatremia) (35).
Sick animals	1. Early normotensive *Escherichia coli* endotoxemia changes the distribution and elimination of balanced crystalloid fluid bolus in rabbits (34). 2. Early or late sepsis induced by *Pseudomonas aeruginosa* bacteremia did not change the PV expansion, distribution, and elimination of a single isotonic crystalloid fluid bolus in sheep (40). 3. Vasoactive agents alter the distribution and elimination of isotonic crystalloid fluid in septic anesthetized sheep (43, 45), similarly to healthy awake sheep (43, 45). a. α_1-adrenergic stimulation worsens peripheral fluid accumulation in septic anesthetized sheep, as urinary excretion is not increased to the same extent as in healthy awake sheep (43, 45).

isotonic crystalloids (26, 27, 60, 66) and normovolemic conscious sheep (36). However, a discrepancy in measured and estimated values resulting in underestimation of V_p was reported in sheep during general anesthesia receiving positive pressure ventilation (36). The most common way to calculate the elimination half-life ($t_{1/2}$) of infused fluid is by utilizing Cl_R which is obtained by dividing urine output with the AUC for the fractional plasma dilution or absolute volume expansion in the clearance or micro-constant model, respectively (30).

CLINICAL AND RESEARCH APPLICATIONS

The use of VK overcomes the limitations of external indicator-dilution techniques for physiologic spaces estimation or measurements of hemodynamic end-points (37). An external indicator distributes within conventional physiological body fluid spaces but may not reflect the effects of IV fluid under dynamic, non-steady state circumstances. Hemodynamic end-points undeniably provide a different set of useful information, but fundamental information about fluid shifts, functional body fluid space volumes, or mechanisms behind differences in fluid dynamics are not assessable. Although VK fluid space models and parameter estimates are less intuitive and describe fluid handling without precisely measuring physiologic spaces, interpreting them in light of mass balance analysis may improve understanding and describe changes in traditional physiologic compartments that are more familiar to both scientist and clinicians (38). The clinical implications of VK analysis in healthy and sick animals are summarized in **Table 2**.

Published Work in Human Literature

There are now more than 60 research publications in human medicine describing the VK of isotonic crystalloids, balanced crystalloids, hypertonic solutions, and colloids under diverse surgical and physiological conditions (30–33). Although first introduced two decades ago, VK studies continue to appear in the scientific literature (70–74, 99–102) and the research method is starting to gain recognition (15, 16), especially in light of the increasing debate on the safety and changing practices of fluid therapy.

The first *in vivo* VK study described the effects of commonly used equipotent IV fluid boluses on the expandable fluid spaces in healthy male human volunteers (mean 80 kg) (26). Balanced crystalloid (25 mL/kg acetated Ringer's solution over 30 min) was found to generate the largest plasma dilution, while the dilutions corresponding to colloidal solution (5 mL/kg 6% Dextran 70 in 0.9% NaCl over 30 min) and HS (3 mL/kg 7.5% NaCl over 30 min) were comparable but with a longer duration of effect (26). Urinary excretion was not measured, and k_{10} (reported as k_r in the original model) was computed by VK modeling (26). This work was further extended to investigate the effects of different balanced crystalloid infusion rates (25 mL/kg acetated Ringer's solution over 15, 30, 45, and 80 min) and volumes (12.5 mL/kg acetated Ringer's solution over 30 min) in healthy female human volunteers (mean 60 kg) (27). Acetated Ringer's solution was discovered to have a more effective and extended plasma expansion effect when infused over a longer time period, and reached a maximum effect of 36% volume expansion (550 mL in an adult human) regardless of infusion rates (27).

Over the years, VK analysis has provided some mechanistic explanations as to why and when patients are sensitive to large volumes of fluid (103). Slow fluid distribution to the peripheral compartment has resulted in a 50–75% larger plasma dilution during a crystalloid infusion than would be expected if the distribution had been immediate (32). In healthy conscious volunteers, isotonic balanced crystalloids are reported to take up to 25–30 min to distribute following rapid IV infusion (25 mL/kg over 30 min) (32). Due to this lag time for crystalloids to

equilibrate between plasma and interstitium (66), PV expansion during the actual infusion is much larger than the commonly suggested expansion of 20–25% of the infused volume (32). Several studies have shown that the immediate PV expansion can be substantial. In a group of normovolemic human volunteers, 50% of a 2 L acetated Ringer's solution given over 20 min was retained within the intravascular compartment at the end of the infusion (66). In a study where acetated Ringer's solution was infused continuously throughout transurethral resection of the prostate in male adults under general anesthesia (104), fluid retention averaged 60% of the infused volume. The fraction of infused fluid that persists in the intravascular compartment is higher for slower infusions (27). Therefore, crystalloids may be better PV expanders than currently acknowledged, provided that the infusion is continuous and not administered as a bolus.

Volume kinetic analysis has also been used to describe the distribution and elimination of isotonic and hypertonic fluids within the body (68). When IV administration of 25 mL/kg of 0.9% NaCl was used as a reference fluid and compared to an equal volume of lactated Ringer's solution, acetated Ringer's solution, 5 mL/kg of 7.5% NaCl, and 3 mL/kg of 7.5% NaCl in 6% dextran solution (HSD), all infused over 30 min, plasma dilution efficiency according to the AUC of dilution-time profiles was found to be 0.88, 0.91, 3.97, and 7.22, respectively in 10 healthy male volunteers (mean 81 kg) (68). Based on VK analysis and simulation, the strength of these respective fluids to dilute the plasma by 20% within 30 min was 0.94, 0.97, 4.44, and 6.15 times greater than of 0.9% NaCl, respectively (68). Urinary excretion was found to be 1.8 times and 2.7 times larger than the infused volume of HS and HSD, which the authors attributed to natriuresis induced by sodium load (68). In this study, comparison between fluids was complicated by the need for several models, including a three-volume fluid space kinetic model for hypertonic fluid, to account for possible osmotic fluid shift (f_t).

In a more recent study (59), the volume effects of 10 mL/kg of 6% HES 130/0.4/9:1 (Voluven®), 20 mL/kg of acetated Ringer's solution, and a combination of HES and acetated Ringer's solution administered 75 min apart was explored using VK in 10 healthy male volunteers (mean 79 kg). The kinetic models were successfully fitted to all experiments using the 1-VOFS kinetic model for HES and the 2-VOFS kinetic model for acetated Ringer's solution. The V_c for HES in both series of experiments was 3.14 L (∼5% of BW), close to the PV estimated by anthropometry, with a $t_{1/2}$ of 2 h (59) similar to the $t_{1/2}$ reported in the product monograph (105). Hydroxyethyl starch was found to induce diuresis with 85% of the infused volume excreted as urine when administered alone (59). The V_c for acetated Ringer's solution averaged 4.88 L (∼6.2% of BW) with a $t_{1/2}$ of 88 min (59), similar to the $t_{1/2}$ of 82 min reported with 2% dehydration induced by furosemide (79). The authors thus attributed the prolonged $t_{1/2}$ to mild dehydration following an overnight fast. The $t_{1/2}$ of acetated Ringer's solution was otherwise reported to average 21 min in euhydrated conscious volunteers (79). When combined with HES, the distribution and elimination of acetated Ringer's solution occurred more slowly than in the single-infusion experiments (59).

Volume kinetic modeling has been used to evaluate IV fluid dynamics using different types of IV fluid solutions (26, 59, 68, 74) and rates (71) in various age groups (106, 107), as well as fluid shifts during inhalation anesthesia (99, 108), epidural anesthesia (109, 110), subarachnoid block (106, 108, 111–113), dehydration (78, 79, 114), hemorrhage (66, 73, 114), acute systemic inflammatory states (72), adrenergic influence (77), perioperative period (115), surgical trauma (96, 116), glucose supplementation (117–119), and pre-eclampsia (120). Through the various VK studies accumulated over the years, the $t_{1/2}$ of various IV solutions can now be summarized and were discovered to be significantly variable governed by multiple factors such as the type of fluid and the patient's physiological conditions, further supporting the importance of clinical context (30). Of note, this body of work has been conducted exclusively by the same group of researchers, perhaps due to the intricacy of these analyses, and VK has not found widespread utilization by other researchers. Several international research teams have published on the development of locally modified mathematical fluid kinetic models (121–124) and external validation attempts of these models (125–127). Microcirculatory exchange models that predict fluid, protein, and small ion distribution in the vascular, interstitial, lymphatic, and intracellular compartments using mass balance equations for fluid and individual solutes along with auxiliary transport equations, instead of plasma dilution, have also been explored (22, 128). These model-predicted fluid volume changes were comparable to published experimental data (129) and clinical data obtained using segmental bioelectrical impedance analysis (22).

Previous Work in Animal Research Models

To date, VK analysis has only been utilized in rabbits (34), pigs (35), and sheep (36–45) which served as experimental research models for human medicine. Sheep and pigs are common biomedical research models for the study of major human physiological systems including the cardiovascular, respiratory, and renal systems due to their well-defined anatomy, physiology, and large body size which permits frequent blood sampling as well as instrumentation with monitoring and sampling devices (130, 131). Translation of experimental work in animal models to humans is feasible, although some species differences exist, such as the reservoir function of the spleen. Thus far, VK modeling and analysis in sheep, rabbits, and pigs appears robust with clinically relevant results that are physiologically sound, providing credibility for wider application to other mammalian species that share similar cardiovascular-renal anatomy and physiologic characteristics.

The distribution and elimination of IV fluids have been investigated under the influence of inhalant anesthesia (36, 38, 42), various fluid infusion rates and duration (37, 39), hemorrhage (41), hypoproteinemia (44), sepsis (34, 40), and use of vasoactive agents (43, 45) in sheep, rabbit, and pig models. Aside from the aforementioned studies performed by the same group of researchers, there is only one veterinary study that investigated real-time IV fluid dynamics using a different method in healthy anesthetized dogs (20). Studies exploring the use of VK in companion animal species could not be identified

following a search of the English literature from the MEDLINE® database using search terms such as "volume kinetic," "fluid kinetic," "fluid dynamics," "fluid behavior," "fluid distribution," "fluid elimination," "fluid half-life," "canine," "feline," "dog," "cat," and "veterinary" via the PubMed®, Europe PubMed Central® (PMC), and Ovid® search engines. Therefore, VK studies in animal research models and the sole canine study form the only basis for additional discussion of fluid dynamics in veterinary medicine.

In 2002, Brauer et al. (36) investigated fluid dynamics of isotonic crystalloid infusion (25 mL/kg 0.9% NaCl over 20 min) in 6 normovolemic splenectomised sheep (mean 42 kg) while under isoflurane anesthesia and while conscious. Using a cross-over experimental design, the 2-VOFS kinetic model revealed that isotonic crystalloid solution was rapidly eliminated from V_c via urinary excretion (median 863 mL, range 604–1122 mL) in conscious sheep; however when anesthetized and mechanically ventilated, urinary excretion was markedly reduced (median 9 mL, range 4–150 mL) resulting in peripheral fluid accumulation (36). Unlike indicator-dilution techniques, VK analysis was able to demonstrate how fluid elimination from V_c transpired more rapidly than accounted for by urinary excretion, thus rather than being excreted, the fluid distributed and accumulated within the peripheral space (38). Plasma volume expansion was otherwise similar for both groups and reached 40–50% fluid efficacy at the immediate end of the infusion despite the marked differences in fluid distribution and elimination (36). Estimated VK parameters correlated well with parameters measured using the indicator-dilution technique with Evans blue dye in the conscious sheep and V_c was 1.6 L (∼4% of BW) (36). However, clearance (reported as k_r) predicted by VK analysis (58.5 mL/min) was significantly different from the manual calculation using median urinary excretion (0.6 mL/min) when sheep were anesthetized and mechanically ventilated (36). Estimates of k_r by VK analysis erroneously underestimated peripheral fluid accumulation by corresponding to the sum of urinary output and extravascular fluid accumulation (36). This led to the discovery that k_r simply reflects net fluid outflow from V_c and does not approximate urinary excretion of infused fluid as previously presumed (26, 27, 60, 109). Unfortunately, the combination of mechanical ventilation and isoflurane anesthesia in the study group precluded separation of individual intervention effects.

A subsequent experimental cross-over study by Connolly et al. (38) in 7 normovolemic splenectomised sheep (mean 28 kg) was designed to discern the effects of isoflurane anesthesia from mechanical ventilation. The study effectively demonstrated that isoflurane anesthesia alone was responsible for significantly decreased urinary excretion and promoting ECF accumulation during isotonic crystalloid volume loading (38). This study was conducted very thoroughly using 4 protocols: conscious spontaneous ventilation, conscious mechanical ventilation through tracheostomy tube, anesthetized spontaneous ventilation, and anesthetized mechanical ventilation. In this study, baseline PV (∼5% BW) increased rapidly during the infusion of 25 mL/kg 0.9% NaCl over 20 min, achieving a 40% fluid efficacy at the immediate end of the infusion (38). This degree of immediate fluid expansion corroborated previous study findings in normovolemic sheep (36) and human volunteers (66). However, despite the initial PV expansion, rapid decline of volume expansion immediately ensued for a duration of 30 min (14% fluid efficacy) followed by a slower phase of decline until the end of the 3 h experiment (4% fluid efficacy) (38). Interestingly, the major findings of Connolly's study were contradictory to a common expectation that positive pressure ventilation alters circulating blood volume and peripheral fluid accumulation by impeding venous return and changing cardiac output (132). The absence of positive end-expiration pressure along with the use of normal tidal volumes (10–15 mL/kg) in euvolemic sheep with healthy compliant lungs may have caused inadequate dynamic changes in intrathoracic pressure and lung volume to induce appreciable cardiovascular effects and secondary fluid shifts. The physiologic mechanism by which isoflurane inhibits diuretic response to volume load and increases extravascular fluid retention has not been determined but reduced glomerular filtration rate and renal blood flow, as well as the involvement of antidiuretic hormone and atrial natriuretic peptide have been speculated to be possible contributing factors (38). A recent matched case-control study of 23 dogs, anesthetized for an elective orthopedic procedure receiving 10 mL/kg/hr of intravenous lactated Ringer's solution for 4 h, reported similar findings of decreased urine output production (<0.5 mL/kg/hr) and substantial peripheral fluid retention as evidenced by significant BW gain, positive fluid balance, as well as increased TBW and ECF volume measured using bioimpedance spectroscopy (133).

Brauer et al. (37) also studied the impact of infusion duration of 0.9% NaCl (6 mL/kg over 5 min, 24 mL/kg over 20 min) and 7.5% NaCl in 6% dextran solution (HSD) (4 mL/kg over 2 min and 20 min) in 6 conscious splenectomised sheep (mean 36 kg). The maximum arterial plasma dilution at the end of the 5 and 20 min 0.9% NaCl infusion were 10 and 22%, respectively. Meanwhile, maximum arterial plasma dilution after 2 and 20 min of HSD infusions were 24 and 21%, respectively. Therefore, the authors concluded that VK variables obtained during a short infusion can be used to predict the outcome of longer infusions, even if the longer infusion also delivers a larger volume (37). This work involving clinically relevant IV fluid doses suggests that VK modeling conforms to linearity such that kinetic parameters obtained can be used to simulate the outcome of other experiments. Subsequently, Svensen et al. (39) published their findings on the VK effects of various isotonic crystalloid infusion volumes and rates (25, 50, and 100 mL/kg of 0.9% NaCl over 20 min) in 6 conscious, splenectomised sheep. Elimination of isotonic crystalloid solution from V_c was found to be proportional to the magnitude of plasma dilution regardless of infused volumes and rates, and elimination occurs via expansion of V_p when renal excretion fails to increase in proportion to the volume of infused fluid (39). Therefore, large and rapid fluid boluses that exceed short-term renal excretory capacity contribute to peripheral fluid accumulation. This study also revealed that markedly supraphysiologic infusion doses exceed the limits of linearity of a VK model.

In 2010, Brauer et al. (44) found that severe acute hypoproteinemia induced by plasmapheresis does not reduce the

PV expansion of isotonic crystalloid infusion (27 mL/kg 0.9% NaCl over 20 min) in non-hemorrhaged, non-splenectomised sheep. The depletion of mean total protein concentration from 5.4 to 2.5 g/dL following plasmapheresis resulted in a parallel reduction in mean plasma COP from 20 to 9.6 mmHg (44). Plasma volume expansion reached ∼20% at the end of the infusion and stayed at 10–15% during the experiment (44). No difference in the PV expansion and cumulative urinary output was found between hypoproteinemic and normal sheep. This is contrary to the conventional physiological reasoning which predicts that a reduction in plasma oncotic pressure will increase fluid filtration, resulting in accumulation of interstitial fluid, reduced plasma protein concentration in capillary filtrate, and increased lymph flow. Splenic contraction and release of RBCs into the circulation affecting the accuracy of plasma dilution calculations were speculated to contribute to the findings however no evidence of hemoconcentration was documented (44), making this explanation less likely. It is intriguing to know if a plasma COP of 50% is sufficient to maintain normal fluid filtration.

The effects of systemic illness have also been explored using VK modeling. Svensen et al. (34) investigated the volume effect of a balanced crystalloid solution (25 mL/kg acetated Ringer's solution over 30 min) in 10 conscious rabbits (mean 4.4 kg) and found that early endotoxemia alters the body's handling of crystalloid solution (34). The expandable volume, V, which represents distribution to the ECF space decreased from 473 ± 37 mL (10% of BW) to 327 ± 54 mL (7.5% of BW), and the rate of elimination (reported as k_r in the original model) increased from 2.9 ± 0.5 to 5.9 ± 2.8 mL/min during early normotensive endotoxemia (34). Visual comparison of individual plasma dilution-time curves demonstrated markedly variable volume effect of acetated Ringer's solution following endotoxin administration. This study provided a glimpse into the net effects of various pathophysiological responses to endotoxemia on the volume effect of IV crystalloid solution, however individual responses that could account for the observed changes could not be isolated. The V of 10% BW obtained in healthy rabbits was in agreement with the size of V obtained in healthy humans (26, 27) but smaller than the anatomical ECF volume (∼20% of BW) to which crystalloids were expected to distribute across.

Almost a decade later, Svensen et al. (40) found contradictory results in a population of septic sheep. The authors found that the distribution and elimination of isotonic crystalloid infusion (25 mL/kg 0.9% NaCl over 20 min) in 6 splenectomised sheep (mean 42 kg) were unchanged by early or late sepsis induced by *Pseudomonas aeruginosa* bacteremia (40). Plasma volume expansion was 312 ± 50 mL (∼29.7% fluid efficacy), 386 ± 34 mL (∼36.7% fluid efficacy), and 400 ± 51 mL (∼38% fluid efficacy) in the control, early sepsis, and late sepsis group (40). Similar peak PV expansion, plasma dilution-time curves, and volume kinetic parameters were obtained for both the control and septic group. These results were contrary to clinical impressions that crystalloid fluid requirements are greatly increased in septic patients due to increased vascular permeability and rapid loss from the intravascular space. The elimination pattern of isotonic crystalloid in septic sheep was similar to control animals and septic sheep also were able to maintain similar levels of PV expansion in response to fluid infusion. The difference between the septic rabbit model (34) and septic sheep model (40) was postulated to be due to the different hypodynamic and hyperdynamic septic shock states that may have been encountered by the models.

Following these studies, fluid dynamics were explored subsequent to administration of vasoactive agents (dopamine, isoprenaline, phenylephrine) in a population of healthy awake sheep (43). Vasoactive drugs were discovered to markedly change the distribution and elimination of crystalloid fluid, thereby altering the PV expansion, urinary excretion, and the risk of peripheral edema (43). An α_1-adrenergic receptor agonist (phenylephrine) was found to promote renal excretion of infused fluid at the expense of fluid distribution to the periphery thus limiting the volume expanding effects of the fluid infusion, while β_1-adrenergic receptor agonist (isoprenaline) had the opposite effect. The interaction between fluid administration and vasoactive drug (norephinephrine, phenylephrine, dopamine, and esmolol) delivery was recently further explored in an experimental sepsis model in sheep (45). Results were similar in most respects to the healthy sheep model (43) in that α_1-adrenergic receptor stimulation with vasoactive drugs accelerated the distribution and elimination of infused fluid, while β_1-adrenergic receptor stimulation retarded the distribution and elimination of infused fluid. Having said that, α_1-adrenergic receptor stimulation did not increase urinary excretion (elimination) to the same extent as it did in healthy awake sheep (43) due to the compounding inhibitory effects of sepsis, general anesthesia, and hypovolemia on diuresis, therefore worsening overall peripheral fluid accumulation (45). In addition, the tendency for peripheral fluid accumulation in the septic sheep model was also pronounced due to the virtual absence of fluid redistribution from peripheral tissues back to the central compartment, in particular when phenylephrine was given (45). The results of this study suggest that crystalloid fluids given in the early phase of sepsis have a marked tendency to accumulate in extravascular peripheral tissues, and drugs that exert a strong stimulating effect on β_1-adrenergic receptors help to limit this aberrant fluid distribution thereby improving hemodynamics through more effective PV expansion.

Aside from the aforementioned animal research models performed by the same research group, there is only one veterinary study that investigated fluid dynamics of various IV fluid solutions in a prospective crossover experimental study involving 4 healthy anesthetized dogs (range 23–25 kg) (20). Silverstein and colleagues utilized a non-invasive continuous in-line hematocrit monitor (Crit-Line^{TM} IIR hematocrit monitor, In-Line Diagnostics, Kaysville, UT) that optically measured hematocrit along an extracorporeal circuit established between a central venous jugular catheter and a cephalic venous catheter to describe the real-time BV changes over 4 h, following rapid IV fluid administration (20). This monitor provides hematocrit value and calculates percent change in BV every 20 s. Each dog served as its own control and received the following treatments

on separate occasions every week: 80 mL/kg of 0.9% NaCl at 150 mL/min, 20 mL/kg of Dextran 70 at 150 mL/min, 30 mL/kg of 6% hetastarch at 150 mL/min, 4 mL/kg of 7.5% NaCl at 1 mL/kg/min, and no IV fluid as control (20). In this study, immediate and rapid increases in BV were described during the infusion of each IV fluid bolus. The volume expansion effect of each IV fluid bolus was directly influenced by the volume of fluid administered, with 0.9% NaCl resulting in the greatest increase in BV (76.4 ± 10.0% change) followed by synthetic colloids (35.9 ± 7.3% change for Dextran 70; 27.2 ± 6.4% change for HES), and finally 7.5% NaCl (17.1 ± 3.2% change) immediately at the end of the infusions (20). Although the volume expanding effect of HS was significantly less than that of any other fluid, its efficiency ratio was the greatest (2.7 ± 0.5) of all the fluids while the efficiency ratio for 0.9% NaCl was the smallest (0.8 ± 0.1). The efficiency ratio for Dextran 70 and HES were 0.9 ± 0.4 and 1.1 ± 0.3 respectively. Upon discontinuing both 0.9% NaCl and HS infusions, the rise in BV ceased immediately with a steep decline in BV for 10 min followed by a more gradual decline thereafter. The fall in BV in the 0.9% NaCl group fell below that of HES by 30 min post-infusion. In contrast, the rise in BV continued for 10 min at the end of colloid infusions and a plateau was observed for the remainder of the experiment. By 240 min, colloidal solutions sustained the greatest volume expansion (25.6 ± 16.1 and 26.6 ± 8.6% for Dextran 70 and HES, respectively) compared to the crystalloid solutions (18.0 ± 9.7 and 2.9 ± 6.1% for 0.9% NaCl and HS, respectively) (20). Similar to VK studies of healthy conscious human volunteers (32), isotonic crystalloid resulted in a substantial BV increase during the infusion period (76.4 ± 10.0% change) and distributed into the ECF compartment by 30 min post-infusion with only ∼25% of the delivered volume remaining within the intravascular space (20).

Following publication of this study by Silverstein and colleagues, IV fluid expansion and retention of differing resuscitative fluids have been widely disseminated in the veterinary literature and textbooks and generalized to the feline species. The use of a non-invasive continuous in-line hematocrit monitor in Silverstein's study was an innovative and unique method which obviated the need for repeated invasive blood sampling, the use of sophisticated mathematical modeling, or isotope administration to estimate BV. However, this method requires placement of a central venous catheter, heavy sedation or general anesthesia, and the use of an extracorporeal circuit which is not practical in the clinical setting, except for patients receiving renal replacement therapies.

LIMITATIONS OF VOLUME KINETICS

As mentioned previously, VK has not found widespread adoption in human medicine due to the complexity of these analyses requiring some mathematical and statistical background, combined with an understanding of biology, pharmacology, and physiology. Volume kinetic modeling and analysis involves specialized PK modeling software that utilizes distinctive PK nomenclature and programming languages which may not be intuitive to the general scientific audience. Data collection is simple and straightforward; however, data analysis and interpretation involve a steep learning curve for those who are unfamiliar with these concepts. Training courses and first-hand utilization of the PK modeling software would be able to accelerate this learning curve.

The main restriction to extensive clinical use of VK is the requirement for repetitive invasive Hb sampling (134). Successive blood sampling over a period of time, usually 3–4 h, is necessary to capture and understand the dynamic fluid flux within the body (32). This presents a greater challenge in veterinary patients who are much smaller with unforgiving blood volumes. A non-invasive modality that could continuously trend a patient's Hb level with accuracy and precision is essential for the safe translation of VK investigation to the clinical population. A continuous non-invasive Hb monitoring device (Radical-7® Pulse CO-Oximeter®, SET V7.4.0.9 and SET V.6.0.1, Handheld R.7.7.1.0, D-station R5.1.2.7, Masimo Corp., Irvine, CA, USA) successfully generated plasma dilution curves and useful kinetic data for group-level human VK analyses, but was unsuccessful in replacing invasive blood sampling due to wide between-subject variation and exaggeration of plasma dilution (134–136). This technology, in terms of hardware and proprietary software algorithms, has been continuously improved over the years; thus, it is worthwhile to reexplore its potential in VK analysis. Unfortunately, this non-invasive Hb monitoring technology is not ready for veterinary use following unsuccessful validation in anesthetized dogs (137) and the lack of published studies in cats.

Mass balance technique using laboratory blood Hb changes has been widely used to estimate intravascular volume status (21, 138–140) but its accuracy has recently been criticized (92, 141) despite past validation against the radio-iodinated serum albumin external indicator-dilution technique (21). Given the possible ripple effect of measurement errors on volume estimation (92), collection of duplicate or triplicate Hb samples, adequate mixing of sampled blood (142), and high-precision laboratory analysis are important to reduce between-sample variability that would affect serial plasma dilution determination and subsequent VK analysis (32).

Recommendations from published VK studies include utilizing a safe yet adequate IV infusion volume, e.g., 20–25 mL/kg crystalloid fluid bolus over 30 min, to minimize "noisy" data and estimation errors associated with very small infusion volumes (32, 92). Many fluid dynamic studies have infused fluids over 30 min to several hours (17, 143) and these prolonged infusion times preclude the differentiation of actual volume effects from distribution-excretion effects (20). Lastly, physiologic variations as a result of a change in body position, splenic contraction and sequestration, dehydration, hypotension, and the use of diuretic or adrenergic drugs, can affect extrapolation of RBC mass to vascular volume changes (20, 32) and should be minimized during the study period. Although of little importance in humans (144), catecholamine-mediated splenic contraction is known to cause a transient increase in hematocrit and BV in dogs, cats, and sheep (31, 145–148) making splenectomy an important consideration in the experimental research setting.

CONCLUSIONS

Volume kinetics is an innovative research method that is gaining recognition for its wealth of accumulated evidence in this new era where clinicians are searching for context-sensitive fluid therapy paradigms. Despite its limitations, the pharmacokinetics of IV fluid therapy is still an appealing concept that has the potential to serve as a new research tool in veterinary medicine to provide insights on the distribution and elimination of commonly prescribed IV fluids. This research method is feasible and deserves a thorough investigation in the companion animal species. The detailed time course of IV fluids within the body, volume expansion effect, efficacy, half-life (duration of effect), and body water physiology in different patient populations under various clinical conditions may allow for more evidence-based IV fluid therapy prescriptions for our veterinary patients. Until a less invasive method of serial Hb monitoring has been validated for veterinary patients, VK will likely remain as a fundamental research tool for modeling and simulation of IV fluid therapy.

AUTHOR CONTRIBUTIONS

XY wrote the first draft of the manuscript. SB, AB, WM, and RH provided critical revision of the manuscript. All authors read and approved the final version of the manuscript to be published.

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NOMENCLATURE

IV	Intravenous
PK	Pharmacokinetics
VK	Volume kinetics
1-VOFS	One-volume fluid space
2-VOFS	Two-volume fluid space
Hb	Hemoglobin (g/dL)
PV	Plasma volume
BV	Blood volume
V_d	Volume of distribution
V	Volume of expandable body fluid space (mL)
v	Volume of expanded body fluid space (mL)
$v - V$	Absolute volume expansion for 1-VOFS model (mL)
$v_c - V_c$	Absolute volume expansion for 2-VOFS model (mL)
$\frac{(v-V)}{V}$	Fractional volume expansion or plasma dilution for 1-VOFS model (mL)
$\frac{(v_c-V_c)}{V_c}$	Fractional volume expansion or plasma dilution for 2-VOFS model (mL)
$V_c = V_1$	Volume of expandable central body fluid space (mL)
$v_c = v_1$	Volume of expanded central body fluid space (mL)
V_d	Volume of distribution (mL)
$V_p = V_t = V_2$	Volume of expandable peripheral body fluid space (mL)
$v_p = v_t = v_2$	Volume of expanded peripheral body fluid space (mL)
Cl	First-order clearance (mL/min)
Cl_R	Renal clearance (mL/min)
Cl_d	Distribution clearance (mL/min)
Cl_0	Zero-order clearance (mL/min)
k_{10}	First-order elimination rate constant (/min)
k_{12}	Central to peripheral intercompartmental rate constant (/min)
k_{21}	Peripheral to central intercompartmental rate constant (/min)
$k_0 = k_b$	Zero-order elimination rate constant (/min)
$R_0 = k_i$	Intravenous infusion rate (mL/min)
AUC	Area under the concentration or plasma dilution-time curve
$t_{1/2}$	Elimination half-life (min)
BW	Body weight
f_t	Translocated volume (mL)
HES	Hydroxyethyl starch
HS	Hypertonic saline
HSD	Hypertonic saline-dextran
MHb	Total hemoglobin mass (g/dL)
NaCl	Sodium chloride
RBC	Red blood cell(s)

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Evaluation of the Distribution and Elimination of Balanced Isotonic Crystalloid, 5% Hypertonic Saline, and 6% Tetrastarch 130/0.4 Using Volume Kinetic Modeling and Analysis in Healthy Conscious Cats

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This prospective, randomized, blinded, interventional cross-over study investigated the distribution, elimination, plasma volume expansion, half-life, comparative potency, and ideal fluid prescription of three commonly prescribed intravenous (IV) fluids in 10 healthy conscious cats using volume kinetic analysis that is novel to veterinary medicine. Each cat received 20 mL/kg of balanced isotonic crystalloid (PLA), 3.3 mL/kg of 5% hypertonic saline (HS), and 5 mL/kg of 6% tetrastarch 130/0.4 (HES) over 15 min on separate occasions. Hemoglobin concentration, red blood cell count, hematocrit, heart rate, and blood pressure were measured at baseline, 5, 10, 15, 20, 30, 40, 50, 60, and every 15 min until 180 min. Urine output was estimated every 30 min using point-of-care bladder ultrasonography. Plasma dilution derived from serial hemoglobin concentration and red blood cell count served as input variables for group and individual fluid volume kinetic analyses using a non-linear mixed effects model. In general, the distribution of all IV fluids was rapid, while elimination was slow. The half-lives of PLA, HS, and HES were 49, 319, and 104 min, respectively. The prescribed fluid doses for PLA, HS, and HES resulted in similar peak plasma volume expansion of 27–30%. The potency of HS was 6 times higher than PLA and 1.7 times greater than HES, while HES was 3.5 times more potent than PLA. Simulation of ideal fluid prescriptions to achieve and maintain 15 or 30% plasma volume expansion revealed the importance of a substantial reduction in infusion rates following initial IV fluid bolus. In conclusion, volume kinetic analysis is a feasible research tool that can provide data on IV fluid kinetics and body water physiology in cats. The rapid distribution but slow elimination of IV fluids in healthy conscious cats is consistent with anecdotal reports of fluid overload susceptibility in cats and warrants further investigation.

Keywords: distribution, elimination, fluid therapy, volume kinetics, crystalloid, hypertonic saline, tetrastarch, cats

INTRODUCTION

The clinical practice of intravenous (IV) fluid therapy in human and veterinary medicine is changing based on new findings (1–3) as well as ongoing debate (4) regarding ideal fluid choice, dose, rate, efficacy, and safety of fluid therapy (4–6). Limited veterinary scientific literature on IV fluid therapy (7) has given rise to empirical fluid therapy recommendations that are based on broad assumptions, historical physiological principles, clinician's anecdotal experiences, or extrapolation from human clinical trials and canine experimental models. Extrapolation of data across species is less than ideal as there may be critical species variations in body water physiology and fluid dynamics associated with different IV solutions. Fluid therapy has the potential to result in fluid overload that increases morbidity and mortality (8, 9), especially in cats (10), yet little evidence exists to support current fluid administration practices in this species (7). The landmark publication reporting increased mortality following standard fluid boluses in African children with severe infection (11) took the medical profession by surprise and subsequently raised many questions regarding our understanding of fluid pharmacokinetics (PK). Since then, there has been a momentous shift in fluid therapy paradigms toward fluid stewardship (12), context-sensitive fluid therapy (13), and treating fluids as drugs (3, 5). Recently, the diverse elimination half-lives ($t_{1/2}$) of balanced isotonic crystalloid and colloid solutions, administered under a wide variety of physiological conditions, have provided further scientific evidence of the importance of context-sensitive fluid therapy (14).

For over two decades, a group of researchers has developed and refined an innovative PK model adapted for body fluid spaces known as volume kinetic (VK) modeling (15–20), providing a mathematical research platform to understand the effects of IV fluid administration on body fluid spaces. Volume kinetics, or in simplistic terms PK of IV fluids, is able to provide descriptive data on the distribution and elimination of IV fluids administered under various physiological conditions in expressions comparable to those employed in conventional PK (18). Visual inspection of the plasma dilution-time curves provides information on the magnitude and time course of plasma volume expansion during and following actual IV fluid infusion (16). Using generated VK parameter estimates, subsequent computer simulation of plasma dilution-time curves allows insight into how IV fluid therapy should be performed (17, 18, 20). With increasing emphasis on safe and responsible fluid prescription, VK is gaining recognition (12, 13) as IV fluids can now be studied like pharmaceutical drugs leading to improved understanding of their time-volume effects or $t_{1/2}$ on plasma and interstitial fluid compartments (14), making evidence-based approaches to fluid therapy possible.

The principles of VK are beyond the scope of this manuscript and readers are directed to current reviews (14, 17, 18, 20). In essence, VK models are designed based on the notion that IV fluid infused at a prescribed rate (R_0) expands the volume of expandable body fluid space (V). Intravenous fluid alters the volume of expanded body fluid space (v) over time as IV fluid is distributed and eliminated from the body fluid space. Elimination occurs in proportion to volume expansion ($v - V$) governed by a first-order elimination rate constant (k_{10}). Distribution of IV fluids can be described using kinetic models analogous to the compartmental models in PK analysis. Intravenous fluid can distribute within a single body fluid space, or be distributed between two body fluid spaces, the central (v_c) and peripheral (v_p) compartment, in proportion to volume expansion of each respective body fluid space governed by first-order bi-directional intercompartmental rate constants (k_{12} and k_{21}). The schematic diagrams of the one-volume fluid space (1-VOFS) and two-volume fluid space (2-VOFS) kinetic models are shown in **Figure 1**.

Although VK has been studied extensively in humans and animal research models (14, 17, 18, 20), this concept is novel in companion animal species and scientific literature is not available. Hence, this preliminary study was designed to answer the fundamental research question of whether VK modeling can be utilized in cats to study IV fluid kinetics and body water physiology in this species. The primary objective of this study was to investigate the distribution and elimination of three commonly prescribed IV fluids [i.e., balanced isotonic crystalloid (PLA), 5% hypertonic saline (HS), and 6% tetrastarch 130/0.4 (HES)] in healthy conscious cats using VK modeling and analysis. The secondary objective was to describe the plasma volume expansion, half-lives, potency, and ideal fluid prescriptions of PLA, HS, and HES. We hypothesized that VK modeling can be applied to healthy cats in a research setting through demonstration of similar peak plasma volume expansion effect when approximately equipotent doses of the aforementioned IV fluids were administered. We further hypothesized that the plasma dilution-time curve of PLA, HS, and HES would be different based on the conventional understanding of the physiological behavior of balanced isotonic crystalloids, hypertonic crystalloids, and synthetic colloids in the mammalian body.

MATERIALS AND METHODS

This prospective, randomized, blinded, three-treatment and three-period (3 × 3) cross-over experimental study was performed at the Ontario Veterinary College, University of Guelph. This study, which required the sampling of ∼24 mL of blood per cat over a duration of 3 weeks, was approved by and conducted in accordance with the guidelines of the University of Guelph's Animal Care Committee. Ten male intact purpose-bred domestic shorthair cats were enrolled into this

Abbreviations: (0), at baseline; (t), at time t; 1-VOFS, one-volume fluid space; 2-VOFS, two-volume fluid space; CI, confidence interval; CV, coefficient of variation; DAP, diastolic arterial pressure; Hb, hemoglobin; HCT, hematocrit; HR, heart rate; HES, 6% tetrastarch 130/0.4; HS, 5% hypertonic saline; IQR, interquartile range; IV, intravenous; k_{10}, first-order elimination rate constant; k_{12}, central to peripheral intercompartmental rate constant; k_{21}, peripheral to central intercompartmental rate constant; LL, log likelihood; MAP, mean arterial pressure; PK, pharmacokinetics; PLA, balanced isotonic crystalloid; RBC, red blood cell(s); SAP, systolic arterial pressure; $t_{1/2}$, elimination half-life; V, volume of expandable body fluid space; v, volume of expanded body fluid space; $v - V$, volume expansion; c, central; p, peripheral; VK, volume kinetics.

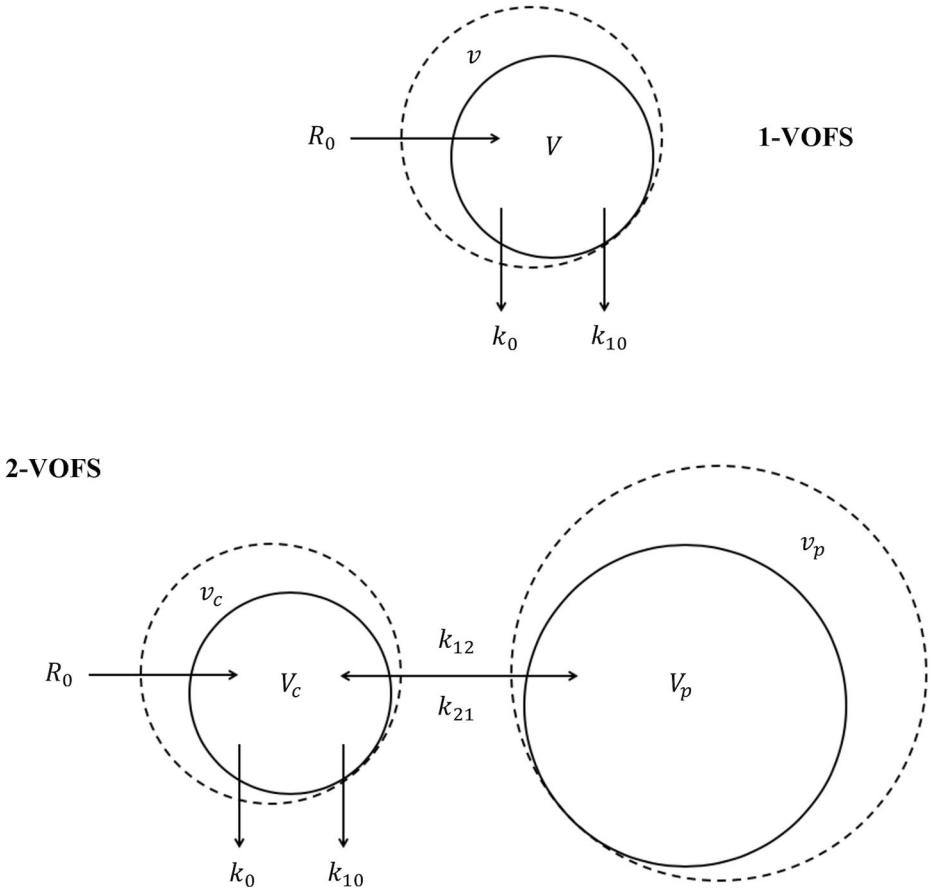

FIGURE 1 | One-volume fluid space (1-VOFS) and two-volume fluid space (2-VOFS) micro-constant kinetic models. Adapted from previous VK work (21–23).

study between June and July 2017. Each cat was certified healthy based on physical examination, complete blood count, serum biochemistry profile, total thyroxine level, urinalysis, symmetric dimethylarginine level, and N-terminal pro B-type natriuretic peptide level. All cats underwent a 7-days acclimatization period and were conditioned to tolerate general handling, simple restraint techniques, and wearing an anti-anxiety shirt[1] as well as light neck bandages. Throughout the entire study period, these cats were fed a commercial dry kibble and had *ad-libitum* access to fresh water.

Instrumentation

Two days prior to the experiment, each cat was instrumented with a central venous jugular catheter[2] under general anesthesia. Sedation included butorphanol[3] (0.4 mg/kg IM) and dexmedetomidine[4] (3 μg/kg IM), followed by propofol[5] induction (2–3 mg/kg IV) and maintenance of general anesthesia using isoflurane[6] in oxygen. Following placement, the central venous catheters were flushed and locked with unfractionated heparin[7] (100 U/mL) according to catheter volume (0.23 mL). Sedation was reversed with atipamezole[8] (equal volume to dexmedetomidine[4] IM). The catheter sites were inspected daily, cleaned as needed with aqueous chlorhexidine gluconate 0.05% solution[9], and the heparin[7] lock was replaced each day throughout the study period. When difficulty or inability to aspirate the catheter was encountered, forceful flushing of the catheter with small volumes of 0.9% normal saline was first attempted. If saline flush was unsuccessful in restoring catheter flow, tissue plasminogen activator[10] (1 mg/mL) was instilled into the partially occluded catheter lumen (0.23 mL) and aspiration was reattempted after a 1-h dwell time. When required, replacement of central venous catheters was performed

[1]ThunderShirt®, ThunderWorks, Durham, NC, USA.
[2]MILACATH® guidewire, single lumen, 20 Ga × 12 cm with integrated extension set, MILA International, Inc., Florence, KY, USA.
[3]Torbugesic®, Zoetis Canada Inc., Kirkland, QC, Canada.
[4]Dexdomitor®, Zoetis Canada Inc., Kirkland, QC, Canada.
[5]Propofol Injection, Fresenius Kabi Canada Ltd., Toronto, ON, Canada.
[6]AErrane Isoflurane USP, Baxter Healthcare Corporation, Deerfield, IL, USA.
[7]Heparin Sodium Injection USP, Fresenius Kabi Canada Ltd., Toronto, ON, Canada.
[8]Antisedan®, Zoetis Canada Inc., Kirkland, QC, Canada.
[9]Sterilin, Inopro Inc., Repentigny, QC, Canada.
[10]Activase® rt-PA, Hoffmann-La Roche Limited, Mississauga, ON, Canada.

at least 24 h prior to the next scheduled experiment using similar technique and general anesthesia protocol.

Experimental Procedure

Food and water were withheld during each 3-h experimental period. Each cat received 50 mg (≤5 kg body weight) or 100 mg (>5 kg body weight) trazodone[11] orally followed by 0.4 mg/kg butorphanol[3] intravenously 90 min later. Following light sedation, a 22-gauge, 1-inch IV catheter was established in the cephalic vein. A low stress environment was maintained throughout the entire experiment with cats wearing an anti-anxiety shirt[1], using feline pheromone[12], and implementation of light and noise reduction.

Each cat received three randomly assigned IV fluid boluses on three separate days with a minimum 72-h washout period between treatments. Intravenous fluid treatment consisted of 20 mL/kg of balanced isotonic crystalloid solution[13] (PLA), 3.3 mL/kg of 5% sodium chloride solution[14] (HS), and 5 mL/kg of 6% tetrastarch 130/0.4 solution[15] (HES) administered over 15 min through the peripheral catheter using a calibrated fluid pump[16]. The fluid doses were selected on the basis of approximately similar volume expansion effect (16). The sodium contents of the prescribed PLA and HS doses were similar, while the prescribed HES dose was based on a 1:4 ratio to crystalloid infusion (24). Subject order and treatment sequences were randomized by an individual independent to the study using an online research randomizer[17]. Fluid delivery was provided by individuals independent to the study such that investigators remained blinded to fluid treatments until data analysis.

Measurements and Data Collection

Duplicate blood samples (0.4 mL × 2) were collected at baseline prior to each fluid administration. Subsequently during IV fluid infusion, single blood samples were collected every 5 min for the first 20 min, then every 10 min until the 60-min time point, and every 15 min thereafter until completion of the 3-h observation period (total of 18 blood samples). At each blood sampling occasion, 0.4 mL of whole blood was collected into a 500 μL ethylenediaminetetraacetic acid (EDTA) microtainer tube and a total of 0.4 mL of saline flush was returned to the cat. Blood samples were collected from the central venous catheter using a three-syringe technique as follows: instillation of 0.2 mL of saline flush followed by aspiration of at least 0.5 mL of diluted blood sample, collection of desired blood sample, then return of initial diluted blood sample followed by an additional 0.2 mL of saline flush. Hemoglobin (Hb) concentration, red blood cell (RBC) count, and hematocrit (HCT) were analyzed by an automated hematology analyzer[18] of an accredited laboratory within 4 h from each blood draw.

At similar time points for blood sampling, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR) were recorded using an oscillometric blood pressure device[19]. During the study, paired sets of longitudinal and transverse cysto-colic ultrasound images were acquired for each cat positioned in dorsal recumbency at baseline and every 30 min throughout the experiment. Urine output measurements were obtained using a novel non-invasive 3-dimensional bladder volume estimation method described elsewhere (25). The average bladder volume estimations from two investigators were used to estimate urine output.

Plasma Dilution Determination

The average coefficients of variation (CV) for Hb concentration and RBC count were determined using the respective duplicate baseline measurements (16). The mean of the duplicate baseline measurements served as the initial baseline values for that experiment. The average plasma dilutions obtained from serial Hb concentrations and RBC counts were calculated using the equation (18, 26):

$$\text{Plasma dilution, } \frac{v_{(t)} - V}{V} = \left[\frac{Hb_{(0)}/Hb_{(t)} - 1}{1 - HCT} + \frac{RBC_{(0)}/RBC_{(t)} - 1}{1 - HCT}\right] \div 2 \quad (1)$$

These calculations were performed using a computer software[20]. To determine whether Hb correction was necessary, three randomly selected experimental data sets were analyzed using plasma dilution calculated from corrected (18) and uncorrected Hb concentrations. The VK data output utilizing plasma dilution with and without Hb correction were compared, and the differences were found to be marginal. Therefore, the reported VK analyses were performed using the uncorrected plasma dilution.

Volume Kinetic Modeling

All data sets, regardless of fluid type, were first analyzed together, and both 1-VOFS and 2-VOFS kinetic models were fitted to the data. Following that, data sets were analyzed separately according to the different fluid types, and both kinetic models were fitted to the data. Sub-analysis of HS infusion was also performed using a three-volume fluid space kinetic model taking into account the effects of osmotic fluid (27). The various kinetic models were compared, and the best model was selected using the log-likelihood test. The differential equation used for the 1-VOFS kinetic model was:

$$\frac{dv}{dt} = R_0 - k_{10}\,(v - V) \quad (2)$$

[11] TEVA Trazodone, TEVA Canada Limited, Toronto, ON, Canada.
[12] Feliway®, CEVA Animal Health Inc., Cambridge, ON, Canada.
[13] PLASMA-LYTE A Injection, Baxter Corporation, Mississauga, ON, Canada.
[14] 5% Sodium Chloride Injection USP, Baxter Corporation, Mississauga, ON, Canada.
[15] VOLUVEN®, Fresenius Kabi Canada Ltd., Richmond Hill, ON, Canada.
[16] VET-PRO VIP 2000™ Veterinary Infusion Pump, Caesarea Medical Electronics Ltd., Staufenburgstr, Lichtenstein, Germany.
[17] Urbaniak, G.C., and Plous, S. (2013). Research Randomizer (Version 4.0) [Computer software]. Retrieved on June 24, 2017, Available online at: http://www.randomizer.org/.
[18] Siemens ADVIA 2120i Hematology Analyzer, Siemens Healthcare GmbH, Henkestr, Erlangen, Germany.
[19] Cardell® Veterinary Vital Signs Monitor, Model 9401, Midmark, Tampa, FL, USA.
[20] MATLAB®, R2013b, MathWorks® Inc, Natick, MA, USA.

The differential equations used for the 2-VOFS kinetic model were:

$$\frac{dv_c}{dt} = R_0 - k_{10}\,(v_c - V_c) - k_{12}\,(v_c - V_c) + k_{21}\left(v_p - V_p\right) \quad (3)$$

$$\frac{dv_p}{dt} = k_{12}\,(v_c - V_c) - k_{21}\left(v_p - V_p\right) \quad (4)$$

Serial plasma dilution and estimated urine output were used as input variables for VK analysis. Estimated urine output was included to stabilize the kinetic models. Intravenous infusion rates (R_0) for PLA, HS, and HES were obtained directly from the prescribed fluid dosages. The average estimated urine outputs measured throughout the study were used to estimate k_{10} as follows:

$$\text{Elimination rate constant, } k_{10} = \frac{\text{Urine output}}{\text{AUC for volume expansion}} \quad (5)$$

The fixed parameters in the VK models, i.e., V_c for the 2-VOFS kinetic model, V for the 1-VOFS kinetic model, as well as the kinetic constants governing fluid distribution (k_{12} and k_{21}) and elimination (k_{10}), were generated using a specialized PK modeling and simulation software[21] for non-linear mixed effects.

Volume Kinetic and Covariate Analyses (Population Kinetics)

Fluid type, SAP, DAP, MAP, HR, age, and body weight were evaluated as potential covariates in the VK model. The continuous variables SAP, DAP, MAP, and HR were evaluated at every time point, while age and body weight were examined once for each individual data set. The first-order conditional estimation with extended least squares (FOCE-ELS) search routine was applied to provide maximum likelihood estimates for fixed and random effects. A search for trends in plots of random effects was also used to identify potentially significant covariates. A covariate was accepted if it significantly improved the curve-fit through reduction of -2 log likelihood (-2 LL) greater than the critical value of 6.64 ($p < 0.01$), the 95% confidence interval (CI) was statistically significant (excludes 1), and the inter-individual variability or coefficient of variation (CV) was <50%.

The influence of statistically significant covariates on VK was simulated using a computer software[20]. The best estimates of the model parameters were then inserted into Equations 2, 3 and 4. The analytical solutions to the differential equations of respective kinetic models were solved using the ordinary differential equations (optODE) function. The goodness-of-fit of the model was illustrated by comparing the observed experimental data with the model predicted data, with and without consideration of covariate effects.

Plasma Volume Expansion, Half-Life, Fluid Potency, and Ideal Fluid Prescriptions

The magnitudes of the plasma volume expansion for PLA, HS, and HES were obtained from the respective plasma dilution-time curves and are presented as percentages. The half-life is represented by $t_{1/2}$ in minutes and was obtained by the equation:

$$\text{Elimination half-life, } t_{1/2} = \frac{\ln 2}{k_{10}} \quad (6)$$

Fluid potency is an expression of fluid activity defined by the volume required to produce an effect of a given intensity. The comparative potencies of PLA, HS, and HES were illustrated using computer simulation of a standardized arbitrary fluid dose using VK parameter estimates generated from the statistically justified models. The ideal PLA, HS, and HES fluid prescriptions to achieve and maintain 15 or 30% plasma volume expansion were also simulated using VK parameter estimates generated from the respective statistically justified models.

STATISTICS

Basic descriptive analysis was performed using an open source online statistical program[22]. The baseline Hb concentration, RBC count, and HCT were normally distributed and reported as mean ± standard deviation. The SAP, DAP, MAP, HR, and estimated total urine output were not normally distributed according to the Shapiro-Wilk test; logarithmic (base 10) transformation improved the data distribution of the estimated total urine output. Therefore, SAP, DAP, MAP, and HR are reported as median and interquartile range (IQR). Estimated total urine output and body weight are reported as mean ± standard deviation, while age is reported as median and range.

Volume kinetic and covariate analyses were performed by an independent individual (RH) using the specialized PK modeling and simulation software[21] for non-linear mixed effects. Data sets from study subjects were analyzed collectively using a population analysis technique. The VK parameter estimates are reported as mean and 95% confidence interval (CI). Statistical significance was set at a $p < 0.01$. Model comparisons were performed, and statistically justified kinetic models were selected based on the reduction of -2 LL > 6.64 ($p < 0.01$). Forward and backward stepwise covariate search was used to identify statistically significant covariates through the reduction of -2 LL > 6.64 ($p < 0.01$).

RESULTS

Ten cats with a median age of 33 weeks (range 27–33) and mean body weight of 4.79 ± 0.69 kg completed all phases of the study with no adverse effects. All cats maintained normal activity levels and good appetite. No vomiting, diarrhea, abnormal respiratory patterns, or other concerning constitutional signs were recorded. Central venous catheters were replaced in four cats over a duration of 3 weeks due to inadvertent catheter dislodgment ($n = 1$), catheter site infection ($n = 1$), and non-salvageable catheter occlusion ($n = 2$). Throughout the study periods, all cats were normotensive with a median SAP of 116 mmHg (IQR 108–124)

[21] Phoenix® NLME™, version 1.3, Certara, St. Louis, MO, USA.

[22] RStudio Team (2018). RStudio: Integrated Development for R. (Version 1.2.1206.2) [Computer software]. Retrieved on April 14, 2019, from http://www.rstudio.com/.

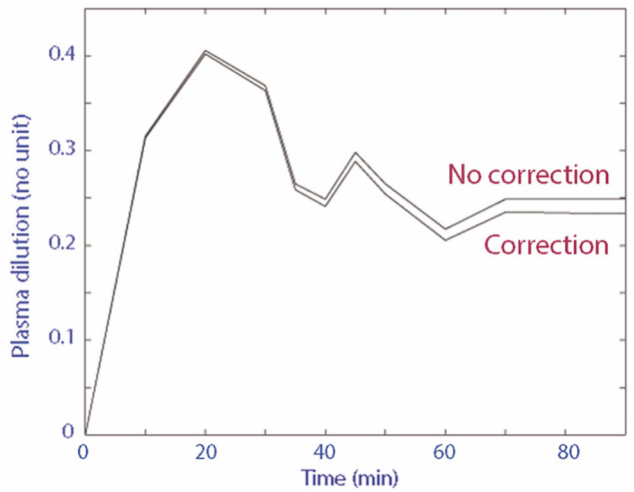

FIGURE 2 | Plasma dilution-time curve with and without correction for Hb loss from serial blood sampling.

and median MAP of 86 mmHg (IQR 74–93; mean 84 ± 17 mmHg). The median HR was 157 beats per minute (IQR 139–187). The mean baseline Hb concentration and HCT at the start of the study were 99.5 ± 11.0 g/L and 30.3 ± 3.4%, respectively. The final Hb concentration and HCT recorded at the end of the study were 76.9 ± 9.5 g/L and 23.8 ± 2.8%, respectively.

Thirty experimental data sets (10 sets of PLA, 10 sets of HS, and 10 sets of HES) were acquired from 10 cats on 3 separate days. One set of PLA data was determined to be unsuitable for inclusion in the analysis based on serial plasma dilution that exceeded three standard deviations from the mean, likely due to spurious baseline measurement. Of the total 540 paired serial Hb concentrations and RBC counts, 37 (6.8%) measurements were removed due to incomplete data and 18 (3.3%) measurements from the unsuitable PLA data set were excluded from further analysis. The average CV for baseline Hb concentration and RBC count were 3.53 and 3.38%, respectively. The estimated total urine outputs for cats receiving PLA, HS, and HES were 37.3 ± 26.5, 16.2 ± 8.4, and 19.5 ± 14.8 mL, respectively. The mean infusion rates (R_0) for PLA, HS, and HES were 6.5, 1.1, and 1.6 mL/min, respectively.

Sample Collection

A total of 18 blood samples (∼8 mL of whole blood) were collected from each cat for every individual experiment. The plasma dilution-time curve with and without correction for Hb loss from serial blood sampling of the three randomly selected experimental data sets diverged very little over time (**Figure 2**). In comparison to uncorrected plasma dilution, VK analysis using corrected plasma dilution ($n = 3$) resulted in lower V_c and higher k_{10} with the differences within an acceptable range of 2–10%.

Group Fluid Analysis

Twenty-nine data sets, regardless of fluid type, were analyzed together, and both 1-VOFS and 2-VOFS kinetic models were fitted to the data. The VK parameter estimates of both kinetic models are summarized in **Table 1**. The goodness-of-fits of urine output and plasma dilution for both kinetic models are illustrated in **Figure 3**. The 2-VOFS kinetic model was statistically justified based on the reduction of -2 LL from 292 to 264 ($p < 0.01$), and thus is considered the better model for group fluid analysis.

TABLE 1 | VK parameter estimates of both 1-VOFS and 2-VOFS kinetic models for group fluid analysis ($n = 29$) in healthy conscious cats.

VK model	VK parameter	Estimate mean (95% CI)	CV
1-VOFS	V, mL	409 mL (280–538)	16.05%
	k_{10}, /min	0.003 /min (0.002–0.004)	17.59%
2-VOFS*	V_c, mL	139 mL (83–195)	20.49%
	k_{10}, /min	0.007 /min (0.004–0.010)	22.76%
	k_{12}, /min	0.326 /min (0.117–0.534)	32.53%
	k_{21}, /min	0.190 /min (0.128–0.252)	16.71%

*denotes statistically justified model based on reduction of -2 LL > 6.64 ($p < 0.01$).
VK, volume kinetic; CI, confidence interval; CV, coefficient of variation; 1-VOFS, one-volume fluid space; 2-VOFS, two-volume fluid space; V, volume of expandable body fluid space; k_{10}, first-order elimination rate constant; V_c, volume of expandable central fluid space; k_{12}, central to peripheral intercompartmental rate constant; k_{21}, peripheral to central intercompartmental rate constant.

In the 2-VOFS kinetic model, covariate analysis identified fluid type and MAP as significant covariates ($p < 0.01$) as supported by the improved residual plots (**Figure 4**). Subsequent sub-analysis demonstrated that fluid type was a covariate to V_c, while MAP was a covariate to k_{12}. With PLA as the reference fluid, the covariances between the different fluid types and V_c were −1.840 (95% CI −2.089 to −1.590) for HS and −1.298 (95% CI −1.621 to −0.975) for HES. Therefore, the V_c of individual fluid types can be expressed as the population V_c to the base of the natural logarithm of the covariance between a specific fluid type and V_c:

$$V_{c\ \text{individual}} = V_{c\ \text{population}}\, e^{\text{covariance (e.g., PLA: 0, HS: } -1.840, \text{ HES: } -1.298)}$$

The covariance between MAP and k_{12} was 0.053 (95% CI 0.029–0.077). The individual k_{12} can be expressed by the equation:

$$k_{12\ \text{individual}} = k_{12\ \text{population}} \left(\frac{MAP_{\ \text{individual}}}{mean\ MAP} \right)^{\text{covariance}}$$

Individual Fluid Analysis

The PLA data set ($n = 9$), HS data set ($n = 10$), and HES data set ($n = 10$) were analyzed separately according to fluid type, and both 1-VOFS and 2-VOFS kinetic models were fitted to the data. Sub-analysis of HS infusion was also performed using a three-volume fluid space kinetic model, taking into account the effects of osmotic fluid shift. The 2-VOFS kinetic model was statistically justified ($p < 0.01$) for PLA and HS, while the 1-VOFS kinetic model was statistically justified ($p < 0.01$) for HES based on the reduction of -2 LL > 6.64. The VK parameter estimates of statistically justified kinetic models for PLA, HS, and HES are summarized in **Table 2**. As depicted by **Figure 5**, the observed

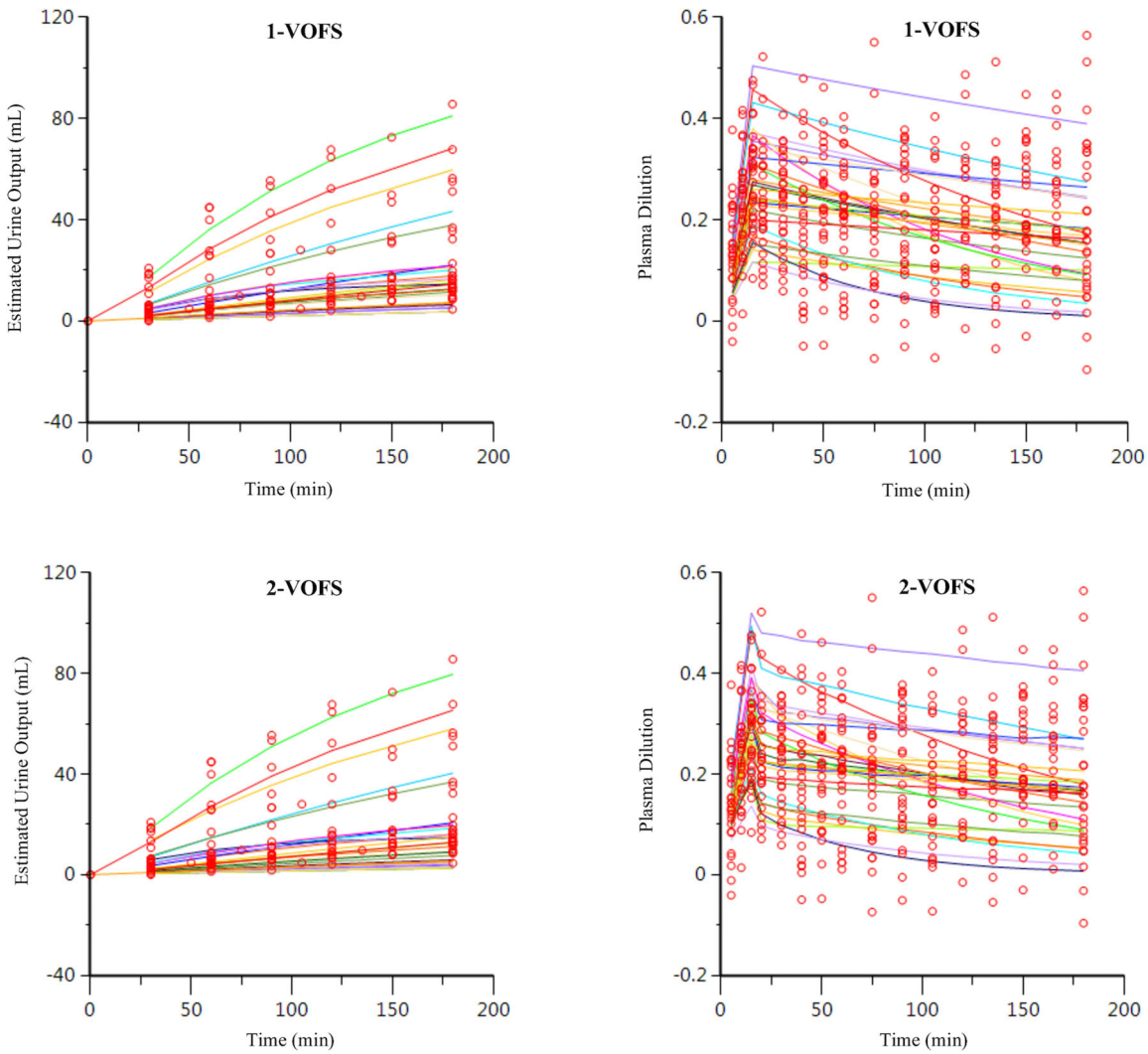

FIGURE 3 | Goodness-of-fit plots of observation (open circles) and individual predictions (colored lines) against time for the 1-VOFS and 2-VOFS kinetic models of group fluid analysis.

urine output values for HS and HES do not fit the values predicted by the statistically justified fitted models.

Covariate analysis for PLA ($n = 9$) demonstrated trends in the plots of random effects, however, none of the tested covariates was statistically significant. The $t_{1/2}$ for PLA was 49 min (95% CI 29–147). On the other hand, MAP was identified as a significant covariate ($p < 0.01$) to k_{10} for both HS and HES with a covariance of −2.865 (95% CI −5.350 to −0.380) and 2.904 (95% CI 0.017–5.790), respectively. The individual k_{10} can be expressed by the equation:

$$k_{10\ \text{individual}} = k_{10\ \text{population}} \left(\frac{MAP_{\ \text{individual}}}{mean\ MAP} \right)^{\text{covariance}}$$

In consideration of MAP as a significant covariate to k_{10}, the $t_{1/2}$ for HS and HES when MAP was 84 mmHg were 319 min (95% CI 188–1054) and 104 min (95% CI 69–213), respectively.

Plasma Volume Expansion and Fluid Potency

The plasma dilution-time curves of PLA, HS, and HES administered at the presumed equipotent doses demonstrated an almost identical peak plasma volume expansion of ∼27–30% (**Figure 6**). Computer simulation of a standardized 6 mL/kg bolus of each solution administered over 15 min using VK parameter estimates generated from the statistically justified 2-VOFS kinetic models for group fluid analysis illustrates the different fluid potencies in **Figure 7**. Of the IV fluids investigated, HS was six times more potent than PLA and 1.7 times more potent than HES. Meanwhile, HES was 3.5 times more potent than PLA.

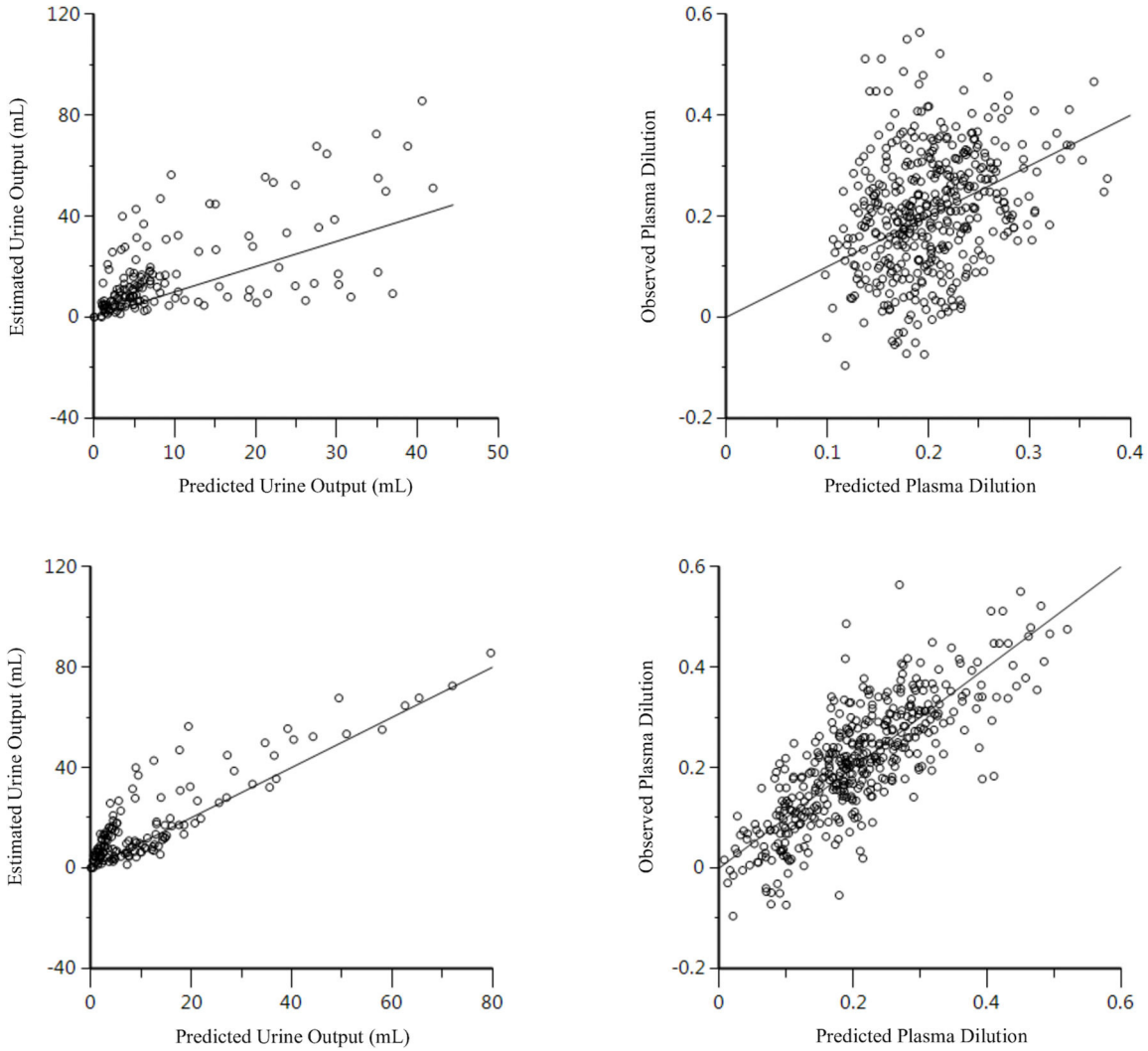

FIGURE 4 | Residual plots for the 2-VOFS kinetic model of group fluid analysis before (top) and after (bottom) considering the covariate effects of fluid types and MAP.

Simulation of Ideal Intravenous Fluid Infusions

The ideal PLA, HS, and HES fluid prescriptions to achieve and maintain 15 or 30% plasma volume expansion in a 5 kg healthy conscious cat simulated using VK parameter estimates generated from the respective statistically justified models are summarized in **Table 3** and **Figure 8**.

DISCUSSION

This exploratory study demonstrated the feasibility and potential of VK modeling and analysis in evaluating the distribution, elimination, plasma volume expansion, half-life, potency, and ideal fluid prescriptions of PLA, HS, and HES in healthy conscious cats using serial Hb- and RBC- derived plasma dilution supported by estimated urine output. All cats successfully completed each phase of the experiment with only minor indwelling central venous catheter complications and tolerated the frequent blood sampling well. The frequency of measurement time points was sufficient to complete the VK analysis, although the 3-h observation period did not capture the entire return of plasma dilution to baseline. Kinetic models were successfully fitted to all experimental data sets and a novel approach of VK analysis, where all fluids were analyzed in a unified model, produced similar findings as the conventional individual fluid analysis approach. Overall, the results generated from this study were logical and physiologically sound. The demonstration of similar peak plasma volume expansion following administration of approximately equipotent fluid doses, as well as half-life and fluid potency that conform to expectations suggest that VK modeling and analysis has the potential to investigate IV fluid kinetics and body water physiology in cats.

TABLE 2 | VK parameter estimates of statistically justified VK models for individual fluid analysis in healthy conscious cats.

IV fluid types	PLA mean (95% CI)	HS mean (95% CI)	HES mean (95% CI)
Sample size, *n*	9	10	10
VK model*	2-VOFS	2-VOFS	1-VOFS
V_c or V	74.25 mL	32.41 mL	80.33 mL
	(28.93–119.57)	(22.11–42.72)	(58.59–102.07)
k_{10}	0.014 /min	0.002 /min	0.007 /min
	(0.005–0.024)	(0.000–0.004)	(0.003–0.010)
k_{12}	0.753 /min	0.141 /min	-
	(0.199–1.308)	(0.018–0.263)	
k_{21}	0.161 /min	0.186 /min	-
	(0.089–0.233)	(0.048–0.323)	

**denotes statistically justified model based on reduction of -2 LL > 6.64 ($p < 0.01$). IV, intravenous; PLA, balanced isotonic crystalloid; HS, 5% hypertonic saline; HES, 6% tetrastarch 130/0.4; CI, confidence interval; n, sample size; VK, volume kinetic; 2-VOFS, two-volume of fluid space; 1-VOFS, one-volume of fluid space; V_c, volume of expandable central fluid space; V, volume of expandable body fluid space; k_{10}, first-order elimination rate constant; k_{12}, central to peripheral intercompartmental rate constant; k_{21}, peripheral to central intercompartmental rate constant.*

Population kinetics is a PK analysis technique that identifies and quantifies sources of variability in substance concentrations between individuals (e.g. age, body weight, physiologic variables, or disease states), which is useful for therapy customization (28). In this type of analysis, all data from all individuals is considered at the same time in a unified model using a non-linear mixed effects modeling approach (29). Although analyzing all fluid types together seems counterintuitive, covariate analysis was able to identify fluid type and MAP as key covariates and determine the degree of variability on the kinetic model. Insertion of relevant covariances into the generated formulas allowed simulation of individual fluids, while a unified model enabled a simplified view of the overall experimental outcome. Analyzing different types of IV fluids together in a unified model has not been previously reported; however, the 2-VOFS kinetic model was successfully fitted to the experimental data and was statistically justified. Regardless of whether group or individual fluid analyses were performed, the overall findings and conclusions were similar, suggesting that multiple approaches to VK modeling and analysis can be considered along with increasing confidence in the models due to their robustness.

When individual fluid analyses were performed, the 2-VOFS kinetic model was better fitted to PLA, while the 1-VOFS kinetic model was appropriate for HES in our population of healthy conscious cats. This is consistent with VK studies of healthy conscious human volunteers (16, 27, 30), except in situations where rapid fluid elimination allowed the 1-VOFS kinetic model to sufficiently describe the kinetics of crystalloid infusions (16, 27, 31). The three-volume fluid space kinetic model was explored for HS however it failed to add notable advantages without compromising model simplicity. The 2-VOFS model was found to be appropriate for HS in our study, similar to the findings in human volunteers (27).

When compared to the individual fluid analysis, the goodness-of-fit plots generated from group fluid analysis revealed better agreement between the observed experimental data and model predicted data, suggesting that group fluid analysis may have more precision. The poor agreement between the observed and model predicted urine output of individual fluid analyses, in particular for HS and HES (**Figure 5**), may be a result of inaccuracies in estimating urine output using point-of-care ultrasonography. However, it is interesting that the imprecisions only involved HS and HES infusions, possibly due to the small volumes of urine generated in these experiments. A second elimination compartment was tested *post-hoc* without improvement of these models, suggesting that the estimated urine output truly represents fluid elimination. Regardless, urine output is not a crucial input variable in VK analysis although it serves to stabilize the VK model, if available (32). Alternative explanations to the discrepancy between estimated urine output and model predicted urine output for HS and HES include increased glomerular filtration rate as a result of fluid shifts from other parts of the body (33), effects of natriuresis (27, 34), or decreased water reabsorption from the presence of filtered oncotic macromolecules (30). The effects of natriuresis are considered less likely given the equimolar sodium ion administered for HS and PLA.

In comparison to healthy humans, the rates of bi-directional fluid distribution from the central to the peripheral compartment (k_{12}) and vice versa (k_{21}), were found to be very fast in our study subjects. The distribution phase of PLA and HS in our healthy cats were between 5 and 10 min (**Figure 6**), at least 3–4 times faster than the reported 25–30 min in healthy human adults receiving crystalloid infusions (18, 35) and healthy anesthetized dogs (36). These findings are based on the plasma dilution-time curves, whereby the distribution phase is represented by the initial steep decline in plasma dilution at the end of the fluid boluses. In humans, the lag time for IV fluids to equilibrate between the plasma and the interstitium allows for cumulative plasma volume expansion up to 50–70% (37, 38) by the end of a fluid bolus. It is possible that fluid distribution occurred while IV infusion was still ongoing in our cats. When IV fluids were analyzed individually in our study, the distribution of PLA from the central to the peripheral compartment was five times faster than HS. We believe this may, in part, be due to the increase in transcapillary hydrostatic pressure and fluid filtration related to the total volume of administered fluid. This rapid distribution phase in healthy cats suggests that cats have a more pliable and compliant interstitial matrix (39) than other species.

Interestingly, in our population of healthy conscious cats, the rate of fluid elimination as described by k_{10} was found to be very slow for all individual fluid types, in contrast to healthy conscious sheep (40, 41) and healthy human volunteers (16, 27, 31). A marked reduction in fluid elimination is reported in anesthetized human patients undergoing various surgical procedures (14, 18), and is also documented in experimental anesthetized sheep (40, 41). When renal excretion fails to increase in proportion to the volume of infused fluid, whether under general anesthesia (40–42) or when subjected to supraphysiologic infusions (43), low fluid elimination augments plasma volume expansion and

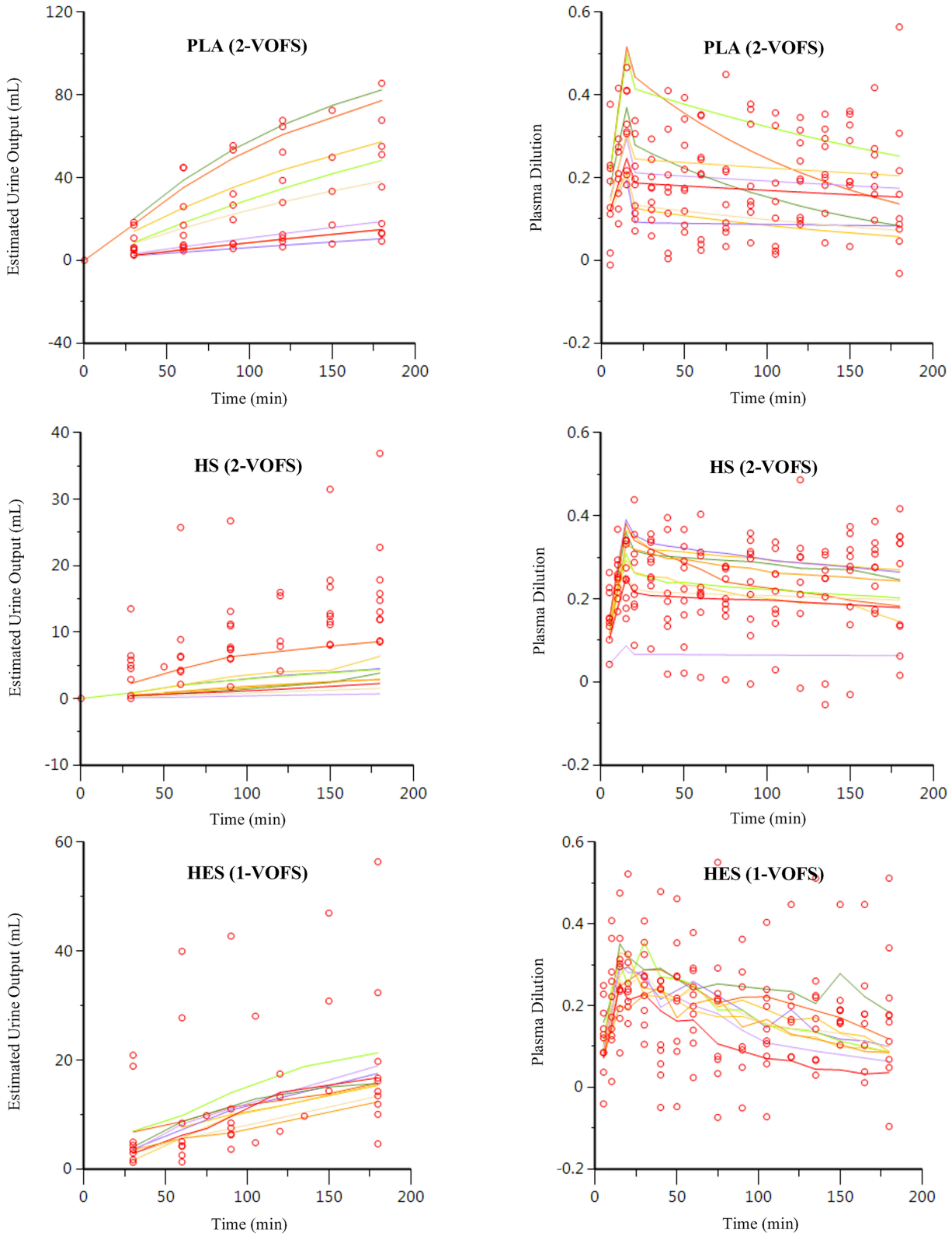

FIGURE 5 | Goodness-of-fit plots of observation (open circles) and individual predictions (colored lines) against time for PLA, HS, and HES using respective statistically justified kinetic models.

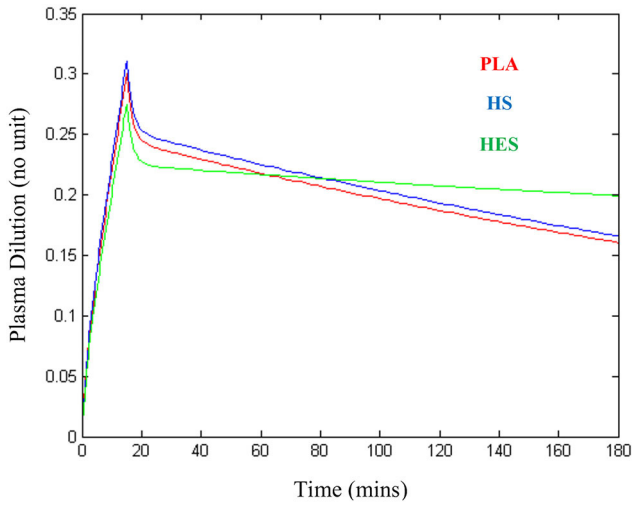

FIGURE 6 | Plasma dilution-time curves illustrating approximately similar peak plasma expansion for 20 mL/kg of balanced isotonic crystalloid (PLA), 3.3 mL/kg of 5% hypertonic saline (HS), and 5 mL/kg of 6% tetrastarch 130/0.4 (HES) administered intravenously over 15 min in healthy conscious male cats.

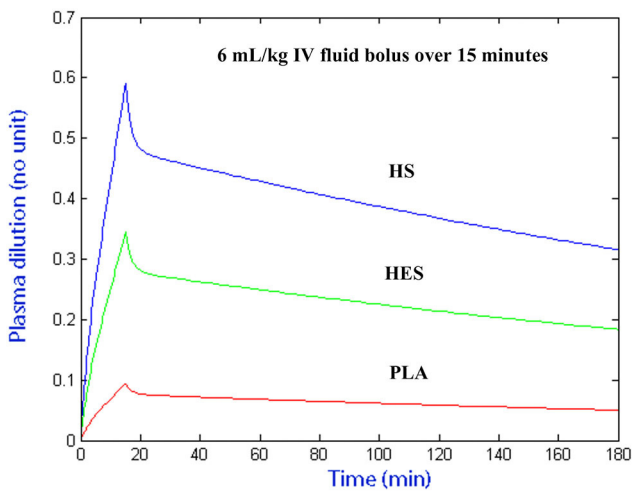

FIGURE 7 | Computer simulated plasma dilution-time curves for PLA, HS, and HES that illustrates the different fluid potencies. Simulation performed using VK parameter estimates generated from the statistically justified 2-VOFS kinetic models for group fluid analysis.

increases the risk of interstitial edema formation from the surplus infused volume.

Furthermore, our data suggest that the rate of fluid elimination for PLA was twice as rapid as HES and up to seven times faster in comparison to HS. The $t_{1/2}$ of PLA, HS, and HES in our population of healthy conscious male cats were found to be 49, 319, and 104 min, respectively. The $t_{1/2}$ of PLA is comparable with studies in human volunteers, where the median $t_{1/2}$ was reported to be between 20 and 60 min depending on gender, stress levels, and hydration status (16, 31, 37, 44–46). For colloids, the oncotic macromolecule $t_{1/2}$ of 130/0.4 HES in healthy human volunteers was discovered to be much prolonged at 12 h (47) and 16 h (48) in those with renal impairment. Of note, these $t_{1/2}$ relate to the HES macromolecules and not the duration of plasma volume expansion, which the latter is of key interest to clinicians. In VK studies performed in healthy human volunteers, the $t_{1/2}$ of 130/0.4 HES which reflected the actual decay of plasma volume expansion was 2 h (16, 30), which is similar to our reported $t_{1/2}$ of 104 min. This is also consistent with the reported systemic circulation $t_{1/2}$ in the product monograph (49). Direct comparison of the $t_{1/2}$ of HS with other studies is not possible due to the different strength utilized in our study. Based on our traditional understanding of the physiological mechanism of HS in the body (33), we expect HS to have a shorter $t_{1/2}$ and more rapid elimination due to the effects of natriuresis (34). However, given that we administered equimolar sodium load for both HS and PLA, the prolonged $t_{1/2}$ of 319 min and slower elimination rate might be as a result of renin-aldosterone-angiotensin-system activation from detection of increased chloride ions.

Although cats remained normotensive throughout the experiments, MAP was found to be a significant covariate for fluid distribution out of the central compartment (k_{12}) in the group fluid analysis, and fluid elimination (k_{10}) for HS and HES. As MAP increases, transcapillary fluid filtration contributes to the increased fluid distribution while stimulation of baroreceptors and activation of renal blood pressure regulation feedback system promotes fluid elimination. The only unexpected finding was a negative covariance between MAP and k_{10} for HS, in which an increase in MAP decreases fluid elimination. The reason for this phenomenon is uncertain at this time.

There are many ongoing debates about the volume efficacy and plasma volume expansion effects of various IV fluids. Data pertaining to the comparative intravascular volume expansion effectiveness of different fluid types in humans and dogs have been thoroughly reviewed (50, 51). Unfortunately, limited scientific data are available in cats, hence we prescribed fluid doses that we considered represented approximately equipotent volume expansion effects. Interestingly, the plasma-dilution time curves of 20 mL/kg PLA, 3.3 mL/kg HS, and 5 mL/kg HES administered over 15 min generated an almost identical peak plasma volume expansion of ∼27–30%. The 4:1 ratio of isotonic crystalloid to colloid appeared to be valid in our population of healthy cats. This is different from the results of recent critically ill human clinical trials (52–55) that showed a cumulative total crystalloid to colloid infusion volume ∼1.2–1.4:1 ratio. When microvascular circulation is considered, our population of healthy cats are thought to have an uncompromised endothelial glycocalyx layer which may have preserved the volume expanding effects of HES (56–58). Conversely, the argument that our large-volume and rapid PLA infusion rate in euvolemic cats may have resulted in direct endothelial glycocalyx damage leading to instantaneous fluid distribution is also possible but considered unlikely since all IV fluid types assessed distributed swiftly in general. Rapid large-volume crystalloid resuscitation has been associated with increased biomarker glycocalyx shedding in a recent canine hemorrhagic shock model (59). Hypervolemia

TABLE 3 | Simulated* IV infusion rates of PLA, HS, and HES to achieve and maintain 15 or 30% plasma volume expansion in a 5 kg healthy conscious cat.

IV fluid types	Desired plasma volume expansion	To achieve *via* 15-min bolus		To maintain *via* CRI	
		(mL/kg)	(mL/min)	(mL/min)	(mL/hr)
PLA	15%	12.0	4.0	0.15	9.0
	30%	24.0	8.0	0.30	18.0
HS	15%	1.8	0.6	0.02	1.2
	30%	3.6	1.2	0.04	2.4
HES	15%	3.0	1.0	0.04	2.4
	30%	6.0	2.0	0.08	4.8

Simulated IV infusion rates, such as these, are important and may be clinically useful for practitioners.
**simulated using VK parameter estimates from 2-VOFS kinetic model of group fluid analysis.*
IV, intravenous; CRI, constant rate infusion; PLA, balanced isotonic crystalloid; HS, 5% hypertonic saline; HES, 6% tetrastarch 130/0.4.

has also been suggested to promote atrial natriuretic peptide release that contributes to endothelial glycocalyx shedding (60), although the subject matter is controversial (61). Plasma atrial natriuretic peptide levels were not measured or investigated in our study.

Following computer simulation of a standardized arbitrary IV fluid dose for all 3 fluids, HS was found to be six times more potent than PLA and 1.7 times more potent than HES, while HES was 3.5 times more potent than PLA. In general, the potencies of these fluids were in line with findings from other human and canine studies (18, 27, 36), albeit experimental differences exist in the use of different strengths of hypertonic saline and types of synthetic colloid solutions. Unlike the previous canine study (36), our study had the advantage of equipotent fluid doses and plasma volume expansion effect, thus removing the confounding effect of total fluid volume administered, allowing direct comparison between individual fluids.

In summary, the data generated from VK analysis in this population of healthy conscious cats support anecdotal reports (10) that cats are more susceptible to the harmful effects of fluid therapy. Our work using this novel approach to IV fluid analysis suggests that cats are different from other species studied, in that commonly utilized IV fluids which we investigated as part of this study protocol distribute more rapidly into the peripheral compartments yet are eliminated more slowly from the body. Low fluid elimination augments plasma volume expansion and increases the risk of interstitial edema formation from the surplus infused volume. This important finding may be the key to the increased susceptibility of this species to fluid overload. Computer simulation using VK parameter estimates generated from pooled and individual fluid analyses highlighted the need for substantial reduction in the constant rate infusion following the initial fluid bolus of all three fluids in order to prevent fluid overload and to maintain the desired plasma volume expansion at steady state. This specific recommendation, however, must be taken in context and is only applicable to healthy conscious euvolemic cats without any ongoing fluid losses. Additional work is warranted to determine the IV fluid kinetics in dehydrated, hypovolemic, or hypotensive cats that represent the clinical population that would be subjected to IV fluid resuscitation followed by ongoing maintenance fluid therapy.

Study Limitations and Future Recommendations

As a preliminary study, our study had a number of limitations. Firstly, the Hb-dilution technique used in this study to quantify plasma dilution has not been validated in cats. This technique, however, has correlated well with other plasma volume determination techniques that utilized radio-iodinated serum albumin (62), blood water desiccation (16), Evans Blue dye (40), and indocyanine green dye (41) in humans and sheep. Secondly, our study subjects were not splenectomised therefore the effect of RBC sequestration and release on plasma dilution determination is unknown. Feline splenic contraction is reported to be brief and transient, lasting only 2 min and reaches a steady-state PCV within 20 min (63). Regardless, initiatives to reduce stress and sympathetic stimulation were implemented throughout each experiment. Recently, the use of trazodone in healthy cats was discovered to significantly decrease systolic blood pressures without resulting in hypotension by reduction of systemic vascular resistance *via* α_1-adrenergic antagonism (64), contrary to previous report in the literature (65) that was available at the time of our study inception. Therefore, it is possible that trazadone may have had some effects on MAP or pre-capillary sphincter tone, and indirectly influenced our study results. Until additional evidence is available, gabapentin may be considered as an alternative oral sedative agent (66) to trazodone to avoid potential influence on fluid kinetics.

As with most veterinary studies, our sample size was small ($n = 10$) but considered acceptable for a preliminary study. For this type of experiment, erroneous baseline measurements had considerable consequences as evidenced by the exclusion of an entire data set even though subsequent serial measurements were appropriate, which further reduced our study sample size. In addition, the average CV of baseline Hb concentration of 3.53% and RBC of 3.38% obtained in our study were higher than the recommended 1% for VK studies (18).

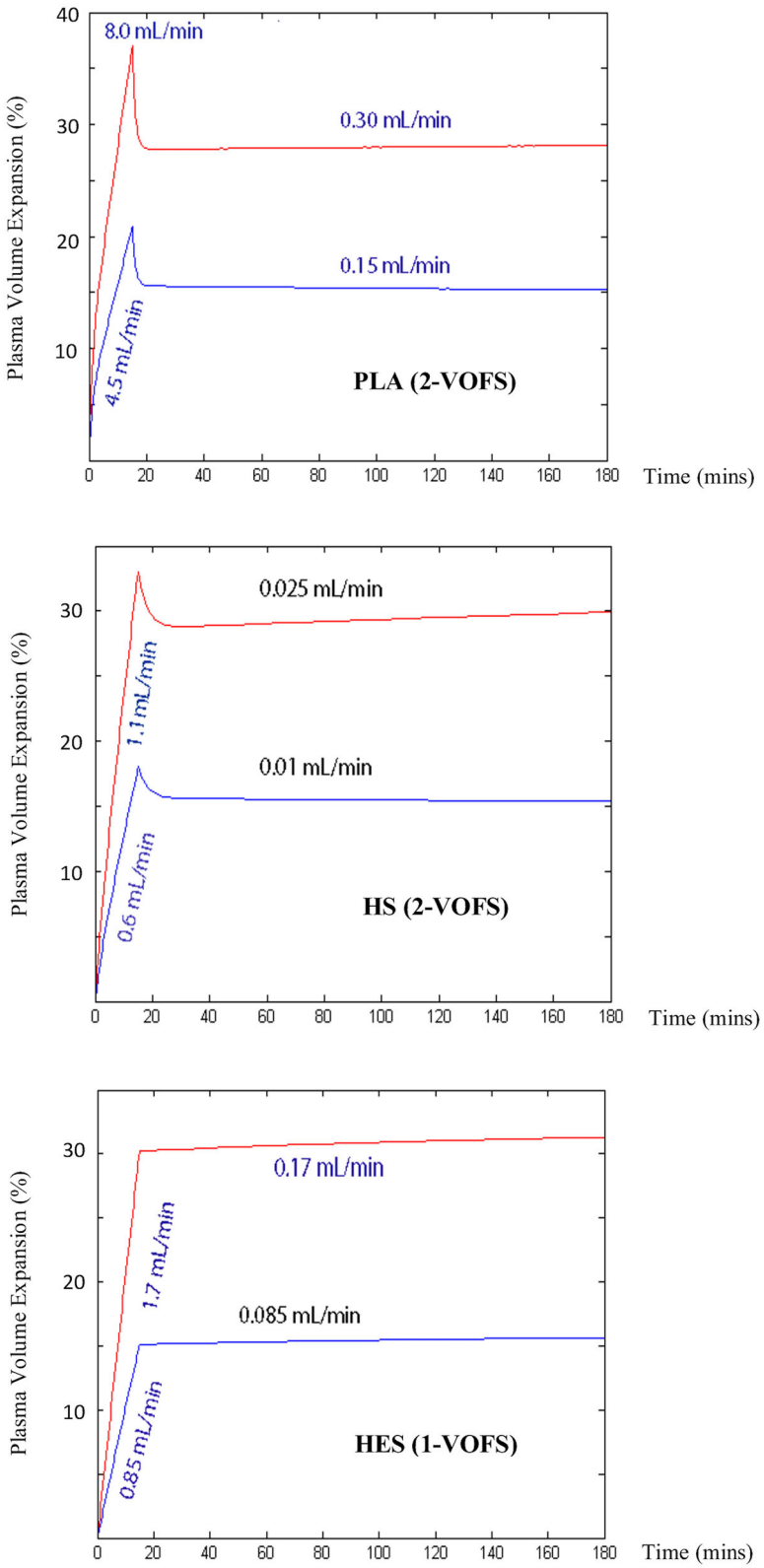

FIGURE 8 | Computer simulated IV infusion rates for PLA, HS, and HES to achieve and maintain 15 or 30% plasma volume expansion in a 5 kg healthy conscious cat. Simulation performed using VK parameter estimates generated from respective statistically justified kinetic models.

Accurate measurements and high-precision laboratory analysis are important to reduce between-sample variability that would affect serial plasma dilution determination and subsequent VK analysis (18). Homogeneity within the sampled blood achieved by adequate mixing is crucial to the quality of analytical results. Specimens idled for over 30 min have a tendency to settle despite anticoagulation and if not thoroughly mixed, Hb values can be overestimated or underestimated depending on whether the concentrated cellular layer or plasma-diluted layer was measured (67). Since simultaneously measured RBCs are diluted similarly as Hb during IV fluid loading but quantified using a different technique by the automated hematology analyzer, the mean value for Hb-derived plasma dilution and RBC-derived plasma dilution was used as the overall plasma dilution to improve precision and accuracy (26). This is important as measurement error was shown to have compounding and exponential effects on serial plasma dilution calculation (68).

For the same reasons above, corrections for Hb loss from blood sampling or hemorrhage have been recommended prior to the curve-fitting procedure as serial blood sampling can result in sufficient Hb loss creating a "false dilution" that is unrelated to IV fluid therapy (18). This, however, was not performed in our study since the blood sample volume at each sampling time point was small (0.4 mL). In addition, an assumption of initial blood volume is necessary to account for sampling losses (17), which meant having to introduce more uncertainties and potential source of error into the model. Although the degree of error associated with the use of varying initial blood volume is acceptable in humans (26, 37), the feline blood volume reported in the current veterinary literature is based on a small number of past experiments (63, 69, 70) and ranges widely from 40 to 66 mL/kg (71, 72) depending on whether cats are splenectomised or not (63, 70). The plasma dilution-time curve of 3 randomly selected experimental data sets did not differ substantively following correction of Hb loss. However, the plasma dilution-time curves continued to diverge gradually over time (**Figure 2**), likely due to compounding effects as more Hb was lost from repetitive blood sampling.

Frequent blood sampling over the duration of 3 weeks led to documented iatrogenic anemia as low as HCT of 20% by the end of the study. The implication of repeated blood sampling was small in our study as each study subject served as their own matched control in a cross-over design and new baseline measurements were established for each individual experiment. Although cats in this cross-over experimental study tolerated the frequent blood samplings well, if unlimited resources are available, a longer between-experiment period should be considered to allow recovery from iatrogenic anemia. However, unless a non-invasive method of serial Hb measurement is developed and validated for VK studies, VK modeling and analysis would likely remain a research tool as the requirement for repetitive invasive Hb sampling precludes it from widespread clinical use. For future studies, we recommend the exploration of non-invasive Hb monitoring technology for potential translation of VK modeling and analysis to the clinical population. Exploration of bioelectrical impedance technology as an adjunct tool to further support and complement the findings of VK analysis is also suggested.

Given that our study subjects came from a homogenous population of healthy male intact young cats, the results of this study cannot be translated to clinical patients. Lastly, VK modeling and analysis can be an inherently complex and sophisticated research method to characterize the PK of IV fluids. To use the information generated effectively, one must possess some mathematical and statistical background, combined with an understanding of biology, pharmacology, and physiology. Data collection is simple and straightforward; however, data analysis and interpretation involve a steep learning curve for those who are unfamiliar with these concepts. However, some coaching and training in these areas would accelerate this learning curve.

CONCLUSION

In conclusion, our study demonstrated that VK modeling and analysis is a feasible research tool that has the potential to provide valuable data on IV fluid distribution, elimination, half-life, plasma volume expansion, fluid efficacy, and body water physiology in cats. The preliminary results generated from VK analysis revealed rapid distribution but slow elimination of IV fluids in healthy conscious cats that is in agreement with anecdotal reports related to susceptibility of cats to fluid overload and warrants further investigation. The prescribed fluid doses of 20 mL/kg PLA, 3.3 mL/kg HS, and 5 mL/kg HES administered over 15 min produced approximately similar peak plasma volume expansion of 27–30%. The half-life and potency of HS was the longest and greatest followed by HES, while PLA had the shortest half-life and was least potent. Simulation of ideal fluid prescriptions to achieve and maintain a 15 or 30% plasma volume expansion at steady state in a 5 kg healthy conscious euvolemic cat revealed the importance of substantial reduction in constant rate infusion following initial IV fluid bolus in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by the University of Guelph's Animal Care Committee (Animal Utilization Protocol 3668) and adhered to the University of Guelph Animal Care Policy and Procedures, the provincial legislation and regulations of the Animals for Research Act, and the national guidelines and policies of the Canadian Council on Animal Care. All individuals with direct animal involvement in this study completed the University of Guelph's Animal User Training Program.

AUTHOR CONTRIBUTIONS

XY, SB, and AB contributed to the conception and design of the study. XY and SB conducted the research. XY acquired and organized the data and wrote the first draft of the manuscript. RH performed the data analysis. XY, SB, and RH contributed to data interpretation. SB, AB, and RH provided critical revision of the manuscript. All authors read and approved the final manuscript.

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Crystalloid and Colloid Compositions and Their Impact

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This manuscript will review crystalloid (hypo-, iso-, and hyper-tonic) and colloid (synthetic and natural) fluids that are available for intravenous administration with a focus on their electrolyte, acid-base, colligative, and rheological effects as they relate to each solution's efficacy and safety. The goal is for the reader to better understand the differences between each fluid and the influence on plasma composition, key organ systems, and their implications when used therapeutically in animals with critical illness.

Keywords: crystalloid, colloid, plasma, osmolarity, fluid therapy, COP, SID, strong ion difference

INTRODUCTION

Water is the body's universal solvent and the most essential nutrient of the body. Within the vessel, water is the transport medium that brings oxygen, solutes, and hormones to the interstitium and removes waste products for breakdown and excretion. Within the interstitial space, water allows movement of these substances between the capillary and the cell. Within the cell, water provides a medium for organelles that gives the cell its form. Water also functions to dissipate heat through evaporation.

Restoring and maintaining fluid balance in the critically ill or injured animal can be one of the most difficult challenges of patient management. Intrinsic factors that dictate the movement of crystalloid fluids into individual body fluid compartments (intracellular, interstitial, intravascular) include the normal distribution of total body water, and the factors involved with the movement of fluids across the capillary membrane (e.g., transmembrane hydrostatic, colloid osmotic pressure, and the endothelial glycocalyx and endothelial membrane integrity), as well as cellular membrane and lymphatic function (1, 2) (editor-See article 2 Advances in the Starling principle and Extracellular Matrix-Compliance?). Fluid composition and volume infused can impact hydrostatic pressure, colloid osmotic pressure (COP) and extracellular fluid osmolality. These changes will ultimately determine the volume kinetics of distribution (3) (editor- See article Volume Kinetics?). An understanding of the fluid types and their unique properties is necessary to ensure that therapy will have the desired effect on the fluid compartment being targeted, and minimize complications associated with fluid therapy.

FLUID TYPES

Crystalloid Solutions

A crystalloid solution is an aqueous solution composed of water and small solutes such as electrolytes and glucose (4, 5). Crystalloid solutions can be categorized based on whether they are hypotonic, isotonic, or hypertonic (**Table 1**). Tonicity describes the effective osmolality of a fluid, which is the ability of a fluid to alter water movement across the cell membrane. It is important to note that fluid osmolality may not equate to tonicity; for example, a fluid can be iso-osmolar and yet hypotonic (see discussion below).

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Hypotonic Crystalloids

A hypotonic fluid has an effective osmolality significantly lower than that of the patient. Infusion will reduce the osmolality of the extracellular fluid resulting in redistribution of water into the intracellular compartment. Dextrose is often added to hypotonic fluids so that they are isosmotic during intravenous administration to prevent hemolysis. However, as the dextrose moves into cells and is metabolized, the fluid becomes hypotonic and they are expected to redistribute to the intracellular compartment based on total body water distribution, i.e., ∼66% of the infused volume of solute-free water will move into the intracellular space.

Hypotonic crystalloid solutions are used for sustaining maintenance fluid requirements, treatment of solute-free water deficits, and drug administration. Maintenance-type crystalloid fluids replace ongoing sensible (measurable; urine, feces, sweat) and insensible (unmeasurable; transepidermal diffusion/evaporation, respiratory evaporation, fever) water lost because of basic bodily functions (6). Solute-free water is lost with insensible losses, and therefore more water than solutes are needed for maintaining fluid balance. Maintenance-type crystalloids have a sodium concentration in the range of 40–77 mEq/L and can contain additional anions and cations (**Table 1**). The osmolality of a maintenance fluid will vary depending on its constituents. The addition of dextrose can make a hypotonic fluid isosmolar at the time of administration. The distribution of maintenance type fluids will expand the intracellular, interstitial and to a minimal extent, the intravascular space. The degree of intracellular vs. extracellular distribution will be dictated by the effective osmolality (tonicity) of the fluid administered.

Dextrose containing solutions that are otherwise solute-free (i.e., do not contain sodium) can be hypo-, iso- or hyper-osmolar depending on the concentration of dextrose in the fluid. They become hypotonic as the dextrose is metabolized leaving solute-free (pure) water. An isosmotic fluid, 5% dextrose in water (D5W) is a source of solute-free water that can be used to treat a solute-free water deficit or as a diluent for drug administration. Although D5W can be used in the treatment of hypoglycemia, caution is needed to avoid iatrogenic hyponatremia. Hyperosmolar dextrose solutions containing 25–50% dextrose can be administered alone (ideally through a central venous line to avoid phlebitis) or added to an isotonic crystalloid solution to provide dextrose supplementation without the risks of hyponatremia.

Isotonic Crystalloids

An isotonic crystalloid fluid has an effective osmolality like the patient. The effective osmolality of common isotonic fluids ranges from 270 to 310 mOsm/L. Isotonic fluids have a similar sodium concentration as the extracellular fluid compartment and have minimal impact on intracellular volume. Isotonic crystalloid fluids can vary in their concentration of the electrolytes sodium, chloride, potassium, magnesium, and calcium (**Table 1**). They may also contain organic anions such as lactate, gluconate, and acetate. The electrolytes and organic anions will contribute to a solutions strong ion difference (SID), and can impact the pH following metabolism of the organic anions (5, 7), except for gluconate, which is mostly excreted unchanged in the kidneys.

A crystalloid fluid is considered balanced if it contains electrolytes in similar concentration to the individual's plasma, maintains or normalizes acid-base balance through its SID, and is iso-osmotic and isotonic to the patient's normal plasma (5, 7). With that definition, there may be few true balanced crystalloid solutions available, since each species and particular patient may vary in their normal plasma make-up. As a fluid is infused, the *in vivo* SID will impact the patient's SID resulting in alteration in the patient's acid-base status. The solution 0.9% sodium chloride is the most unbalanced isotonic crystalloid, given its high, un-physiologic, chloride concentration and its 0 value SID (5, 7). For the purposes of this article, "balanced" isotonic crystalloids will be referencing those traditionally named as such, i.e., Plasma-Lyte 148 and lactated Ringer's solution (LRS).

Isotonic crystalloids are used to replenish extracellular fluid deficits, and as discussed below, to maintain extracellular fluid volume. The volume kinetics of isotonic crystalloids is variable and influenced by the rate of infusion, patient's physiological condition, degree of dehydration, surgery, and anesthesia (see section on volume kinetics) (8, 9). This distribution will be altered with changes in COP, vascular permeability, and changes in the extracellular matrix. Up to 50% of the intravascular volume effect can be lost in as little as 30 min in people with normal transcapillary fluid dynamics (i.e., no hypotension, altered capillary permeability, etc.) (8). The volume of distribution of isotonic crystalloids between the intravascular and interstitial space in health will approximate the relative size of each compartment i.e., ∼25% will remain intravascular, 75% will remain interstitial. Examples of conditions where an isotonic crystalloid is used most effectively include dehydration, hemorrhage, vomiting, diarrhea, and effusive diseases.

Hypertonic Crystalloids

A hypertonic fluid is a fluid that has an effective osmolality (tonicity) greater than that of the patient. Infusion will increase the osmolality of the extracellular fluid resulting in redistribution of water out of the intracellular fluid compartment, increasing extracellular volume. Common hypertonic solutions used in veterinary medicine include hypertonic saline (HTS) and mannitol. The volume effects of these solutions are short lived, since the small solutes will be redistributed and/or excreted.

Hypertonic saline is available at various concentrations, with 3%, 7.2–7.5%, and 23.4% being commonly available. The 23.4% HTS is not recommended for direct infusion and should be diluted before administration. Hypertonic saline in the 3–7.5% range can be infused without dilution or in combination with isotonic crystalloids and/or colloids for hypovolemic shock resuscitation (editor-see articles 10 and 11 Fluid resuscitation in critical ill non-hemorrhage hypovolemic animals and What are the dose response effects of IV fluids following hemorrhage and hemorrhage and trauma?).

Hypertonic saline is also used for customizing crystalloid fluid solutions to target a desired sodium concentration, most commonly for the treatment of patients with dysnatremia. In addition, mannitol and HTS can be prescribed for patients

TABLE 1 | Characteristics of commonly used intravenous fluids.

NAME	OSMOLARITY* (mOsm/L)	pH	Na+ (mEq/L)	Cl- (mEq/L)	K+ (mEq/L)	Mg++ (mEq/L)	Ca++ (mEq/L)	Dextrose (g/L)	Organic anion (mEq/L)	COP (mmHg)	SID (mEq/L)
CRYSTALLOID											
Hypertonic											
7.2% saline	2,396		1,197	1,197	0	0	0	0	0	0	0
Isotonic											
0.9% Saline	308	5.0	154	154	0	0	0	0	0	0	0
Lactated Ringer's	275	6.5	130	109	4	0	3	0	Lactate (28)	0	27
Plasma Lyte-A®	294	7.4	140	98	5	3	0	0	Acetate (27), Gluconate (23)	0	27–50
Plasma Lyte-148® or Normosol-R®	294	5.5	140	98	5	3	0	0	Acetate (27), Gluconate (23)	0	27–50
Sterofundin®-Iso	309	5.5–5.9	145	127	4	2	5	0	Acetate (24), Malate (5)	0	25.5
Hypotonic**											
Plasma Lyte-56 in 5% dextrose®	363	3.5–6	40	40	13	3	0	5	Acetate (16)	0	16
0.45% Sodium chloride + 2.5% dextrose	280	4.5	77	77	0	0	0	25	0	0	0
5% Dextrose in water	252	4.0	0	0	0	0	0	50	0	0	0
0.45% Sodium chloride	154	5.6	77	77	0	0	0	0	0	0	0
COLLOID											
Natural											
Whole blood	300	Variable	140	100	4	0	0	0–4	0	20	
Frozen plasma	300	Variable	140	110	4	0	0	0–4	0	20	12
25% Human serum albumin			0	0	0	0	0	0	0	200	
5g Lyophilized canine albumin			0	0	0	0	0	0	0		
Synthetic											
6% Hetastarch 450/0.7 Hespan™	310	5.5	154	154	0	0	0	0	0	26	0
6% Hetastarch 450/0.7 Hextend™	304	5.9	143	124	3	0.9	5	0.99	Lactate (28)	31	28
6% Pentastarch 200/0.5 HAES-steril 6%™	308	5.0	154	154	0	0	0	0	0	30–35	0
10% Pentastarch 200/0.5 HAES-steril10%™	308	5.0	154	154	0	0	0	0	0	25	0
6% Tetrastarch 130/0.4 VetStarch™ Voluven™	308	4–5.5	154	154	0	0	0	0	0	37	0
6% Tetrastarch 130/0.42 Tetraspan™	296	5.6–6.4	140	118	4	1	2.5	0	Acetate (24), Malate (5)	40	

**The value provided is the calculated osmolarity which may overestimate the measured osmolality of the fluid. The osmolarity of a solution is relevant to the impact on erythrocytes on infusion while the effective osmolality (tonicity) will dictate the volume of distribution of the fluid.*

***These solutions are either hypotonic at the time of infusion, or become so when the dextrose is metabolized.*

COP, Colloid osmotic pressure; SID, Strong ion difference in vivo.

TABLE 2 | Characteristics of commonly used hydroxyethyl starch products.

Hydroxyethyl starch product	Commercial name	Average molecular weight (kDa)	Molar substitution	C2:C6 ratio	COP (mmHg)
6% Hetastarch 450/0.7	Hespan™	450	0.7	4.5:1	26
6% Hetastarch 450/0.7	Hextend™	450	0.7	4.6:1	31
6% Pentastarch 200/0.5	HAES-steril 6%™	200	0.4–0.5	5:1	30
10% Pentastarch 200/0.5	HAES-steril10%™	200	0.4–0.5	5:1	66
6% Tetrastarch 130/0.4	VetStarch™; Voluven™	130	0.4	9:1	36

with signs of intracranial hypertension (editor- see article 12 on TBI?). Hypertonic saline effects include increasing plasma osmolality and sodium and chloride concentration, endogenous release of vasopressin, and immunomodulation (10–13). The impact of infusing a supraphysiologic dose of chloride should be considered, although a direct link between HTS and risk of acute renal injury has not been established (10).

Colloid Solutions

A colloid solution contains large molecular weight particles such as proteins or hydroxyethyl starches (HES) suspended in a crystalloid solution (4). The large insoluble molecules do not easily cross the endothelial glycocalyx and membrane. The force exerted on the endothelial surface layer due to the osmotic gradient created by these proteins is called COP or oncotic pressure. Colloid solutions can be divided into natural and synthetic colloids.

Natural Colloids

Natural colloids are protein-containing products, such as whole blood, plasma, and concentrated albumin solutions. Although any protein can contribute to COP, albumin (∼67,000 Daltons), is most relevant because it is the smallest and most numerous of the protein particles, and, the overall negative charge of albumin attracts positive sodium molecules into its orbit, thereby increasing its osmotic capability by ∼20% (the Gibbs-Donnan effect) (14–16). Albumin also has antioxidant properties, scavenges oxygen-free radicals, and is a carrier protein for steroids, drugs, bilirubin, fatty acids, and hormones (15, 17).

Plasma can be stored as fresh frozen plasma (FFP), frozen plasma, liquid (refrigerated) plasma, cryosupernatant (cryopoor), or stored whole blood. The concentration of albumin in these products will depend on the albumin concentration of the donor animal and is ∼2.5–3 g/dL (18). Of the plasma products, cryoprecipitate does not contain albumin. The choice of the optimal plasma product for a patient will depend on other patient factors such as coagulation status as well as product availability. The volume of plasma products needed to increase albumin levels and provide effective COP support often exceeds product availability or is cost prohibitive. Calculation of albumin deficit demonstrates that ∼45 ml/kg of plasma is required to increase serum albumin by 1 g/dL, assuming there are no ongoing albumin losses.

Lyophilized canine albumin is stored in a dehydrated powder form and reconstituted with 0.9% sodium chloride or 5% dextrose in water to a desired albumin concentration (5–16%). Infusion of a 16% solution (16 g/dL albumin) results in an ∼1.2 times volume expansion. It seems well-tolerated, can increase serum albumin concentrations in dogs with septic peritonitis, and can increase albumin and COP in healthy dogs (19, 20).

Human serum albumin (HSA) concentrates are reconstituted to contain 5–25% albumin. The high concentration of albumin and resulting high COP (200 mmHg) in 25% HSA (25 g/dL albumin) has the greatest capability of increasing plasma albumin and COP (21), however acute and delayed hypersensitivity reactions have been reported in dogs, which can be fatal (18, 22, 23). Infusion of HSA has been done in critically ill dogs and cats to increase serum albumin without reports of hypersensitivity reactions (24, 25).

To estimate the volume of a transfusion product required to increase serum albumin the following formula can be used (26).

Albumin deficit (g) = 10 [0.3 × body weight (kg) × (target albumin concentration (g/dL) − patient albumin concentration (g/dL))].

Synthetic Colloids

Synthetic colloids include gelatins, starches, dextrans and complex polysaccharides. Gelatins and dextrans are infrequently used. Hydroxyethyl starch is one of the most common type of synthetic colloid in use in veterinary medicine. It is a synthetic polymer of glucose (98% amylopectin), made from a waxy species of plant starch such as maize, potatoes or sorghum (27). It is a highly branched hydrophilic polysaccharide closely resembling glycogen, formed by the reaction between ethylene oxide and amylopectin in the presence of an alkaline catalyst. The HES product varies in molecular characteristics and these will determine the clinical effects including half-life, coagulation effects, impact on COP and volume expanding effects. The main characteristics of HES that are relevant are the concentration, molecular weight (MW), molar substitution, and C2:C6 ratio (**Table 2**) (27, 28). The concentration influences the COP and hence the volume expanding effects.

Hydroxyethyl starch contains a polydisperse number of molecules with different MW. The MW impacts the osmotic pressure and the half-life of the product as well as the coagulation effects. Small MW molecules that are below the renal threshold (<70 kDa) will be renally excreted and the intravascular expanding effects are quickly lost. Higher MW molecules have greater impact on coagulation, and this will limit the safe daily

dose of the product. Tetrastarches have a medium MW and have been shown to have less coagulation effects in comparison to an equal dose of the high MW hetastarch products (29), although at low doses this may not be clinically relevant (30) (editor- See Article 7 Colloids, Yes or No? Pros and Cons of Colloids?).

The molar substitution is the calculated average number of hydroxyethyl groups per glucose residue in the molecule. It can be adjusted by the degree of substitution of hydroxyl groups with hydroxyethyl groups at the C2, C3, and C6 positions on the glucose molecule (27). The C2:C6 ratio indicates the degree of substitution of hydroxyethyl groups on position C2 in relation to C6 of the glucose molecule. The higher the molar substitution and the greater the C2:C6 ratio, the slower the degradation of the molecule by amylase. For example, hetastarch 450/0.7 has an average MW of 450 kDa and molar substitution of 0.7 (hence "heta") and has a longer half-life than tetrastarch 130/0.4, which has an average MW of 130 kDa and a molar substitution of 0.4 (hence "tetra"). The HES products are suspended in an isotonic crystalloid solution that vary in constituents as described in **Tables 1, 2**.

Degree of volume expansion and longevity of HES, or any colloid, in plasma is difficult to predict. It will depend not only on the degree of vascular injury, but also on the MW and dispersity, amylase concentration, elimination rate into the urine, as well as its electrical charge, shape, and effect on the endothelial glycocalyx (31–37). Studies focusing on the immunologic, coagulation, and renal effects of HES products are not all in agreement, and species differences may exist (editor- See Article 7 Colloids, Yes or No? Pros and Cons of Colloids?).

FLUID CHOICE

Despite IV fluids being commonly prescribed medications in human and veterinary medicine, the optimal fluid choice remains poorly defined. There is growing evidence in human medicine that fluid choice can have an impact on outcome, particularly in critically ill patients. Specific recommendations for the single best type of crystalloid or colloid fluid to infuse cannot be made based on current information. Patient factors to be considered when selecting an IV fluid type include volume of administration, the patient's electrolyte and acid-base status, and ongoing disease processes. Fluid factors to be considered include tonicity, electrolyte and organic anion concentration, and compatibility with drugs or other fluids that will be co-administered.

Replacement vs. Maintenance Fluids

Maintenance-type fluids were designed to replace solute-free water and electrolyte losses in the otherwise healthy, fasting patient. The composition of maintenance fluids was determined from research performed in healthy children, and the electrolyte composition was determined to resemble the electrolyte composition of milk (38, 39). The water and electrolyte requirements of healthy dogs and cats is described by the National Research Council and these differ greatly from the composition of commercially available fluids (40, 41).

It has been advocated that isotonic crystalloids are given to replenish any extracellular fluid deficits and replace ongoing losses while maintenance type (hypotonic) fluids are given for daily maintenance needs. This requires two fluid types which can increase cost, and clinical experience has shown that most patients can be adequately managed with an isotonic crystalloid alone. Maintenance-type fluid therapy alone may be considered in the patient that has adequate intravascular and interstitial fluid volumes without ongoing extracellular volume losses. An example may be the cat that sustained a jaw fracture and is unable to drink water. Maintenance type fluids may also be considered in the patient that is developing hypernatremia, although adequate support of extravascular volume should be monitored. As maintenance type fluids have less effect on extracellular fluid volume than isotonic crystalloids, they have been favored in patients at risk of volume overload, such as animals with heart disease or kidney disease.

Careful consideration should be taken when prescribing maintenance type fluids for the treatment of sick patients that have extracellular fluid deficits and/or ongoing abnormal losses. The major adverse events that may be associated with the administration of maintenance type fluids are ineffective intravascular volume support and hyponatremia. Acute, hospital acquired hyponatremia has been associated with the administration of hypotonic, maintenance type fluids in human patients (39, 42, 43). Randomized controlled trials comparing isotonic crystalloids with hypotonic crystalloids as ongoing maintenance fluid therapy in adult humans and pediatric patients have shown isotonic crystalloids to be safe and is associated with a lower incidence of hyponatremia (44–47).

Sodium Concentration

As **Table 1** shows, there is a wide range of sodium concentration in the commonly used IV fluids. For most clinical scenarios, balanced isotonic crystalloids (e.g., LRS, Plasma-Lyte 148) are recommended. Although these fluids have a slightly lower sodium concentration than normal dogs and cats, they are considered isotonic in clinical practice. However, animals suffering intracranial hypertension may benefit from receiving an isotonic fluid with a higher sodium concentration (e.g., 0.9% sodium chloride) (editor- see article 12 TBI?).

When treating animals with an abnormal sodium concentration the general guideline is to avoid changing the sodium concentration rapidly (48). When administering large volumes of fluids rapidly to animals with a significant dysnatremia, it is recommended to use a fluid with a sodium concentration within ∼10 mEq/L of the patient. It is generally considered safe for patients with a sodium concentration up to 165–170 mEq/L to receive 0.9% sodium chloride. If a patient with a sodium concentration >170 mEq/L requires rapid administration of large volumes of fluid, it may be best to make fluid prescription isotonic to the patient by the addition of hypertonic saline.

Lactated Ringer's solution is an ideal fluid for patients with hyponatremia unless they have a sodium <120 mEq/L. In that situation, if large volumes of fluids are indicated, it may be necessary to further dilute the sodium concentration with water to make a fluid prescription that is isotonic to the patient.

Chloride Concentration

Balanced isotonic crystalloid solutions have a chloride concentration similar or slightly less than healthy dogs and cats while 0.9% sodium chloride and HES in 0.9% sodium chloride have a higher chloride concentration than normal dogs and cats. Human medicine has traditionally used 0.9% sodium chloride rather than balanced isotonic crystalloids for fluid therapy, and in more recent years the incidence and potential adverse effects of hyperchloremia has been a focus of many investigations.

Chloride has several important physiological roles including regulation of glomerular filtration rate, blood pressure responses, gastrointestinal function, and acid-base homeostasis. The impact of hyperchloremia was demonstrated by a study in a human ICU that evaluated the effect of changing fluid therapy from a chloride-liberal approach (infusing 0.9% sodium chloride or colloids suspended in 0.9% sodium chloride) to a chloride-restricted approach (infusing Hartmann's, Plasma-Lyte 148, etc.) (49). The incidence of hyperchloremia and metabolic acidosis was significantly decreased with the chloride-restricted fluid approach. In a randomized clinical trial, the administration of balanced crystalloids resulted in a lower mortality rate and lower rates of renal replacement therapy or renal dysfunction in critically ill patients, when compared to saline administration (50). In comparison, no difference in outcome could be demonstrated in a similar study of non-critically ill adults (51). In a large veterinary study of all dogs and cats with a serum chloride measured, hyperchloremia was identified in 21% of dogs and 9% of cats and was associated with a higher mortality than those with normochloremia (52).

Potential mechanisms for the harmful effects of administration of chloride rich fluids include altered cytokine responses, increased nitric oxide levels, hemodynamic instability and altered renal blood flow (53). Hyperchloremic metabolic acidosis has been shown to decrease renal blood flow and some studies have found an association with acute kidney injury. Rapid administration of 2 L 0.9% sodium chloride to healthy human volunteers caused a significant reduction in renal arterial blood flow and renal cortical tissue perfusion, when compared to baseline and to the people who received Plasma-Lyte 148 (54). An experimental dog study demonstrated that renal vasoconstriction is a direct result of hyperchloremia (55). Increased renal tubular chloride concentration has been shown to cause increased absorption of chloride by the macula densa leading to afferent arteriolar vasoconstriction. Fluid retention in the interstitial space is also greater with 0.9% sodium chloride than with balanced isotonic solutions. This may further limit urine output and contribute to organ dysfunction. Despite these concerns, the relationship between hyperchloremic metabolic acidosis and kidney injury is not clear and there appears to be a difference in the impact of hyperchloremia in the critically ill patient population. The exact relationship between hyperchloremia and outcome remains to be determined but avoiding iatrogenic hyperchloremia is a strong clinical recommendation at this time.

Hypochloremic metabolic alkalosis is not uncommon and is usually the result of selective gastric loss of hydrochloric acid from abnormalities such as pyloric outflow obstruction. In this case, 0.9% sodium chloride is the ideal fluid therapy as it will increase serum chloride concentration effectively and promote bicarbonate excretion by the kidney to enhance the normalization of acid-base balance.

TABLE 3 | Guideline for potassium supplementation for hypokalemia.

Patient potassium	Rate of potassium administration
Normal to mild hypokalemia (>3.5 mEq/L)	0.05–0.1 mEq/kg/h
Moderate hypokalemia (2.5 to 3.5 mEq/L)	0.3 mEq/kg/h
Severe hypokalemia (<2.5 mEq/L)	0.4–0.5 mEq/kg/h

Potassium Concentration

Since 0.9% sodium chloride contains no potassium, it is commonly recommended for use in patients with hyperkalemia. Potassium homeostasis is impacted by extracellular sodium concentration as well as potassium concentration with sodium-potassium exchange having an important influence. The small quantity of potassium in balanced isotonic crystalloids such as LRS or Plasma-Lyte 148 is outweighed by the benefit of the lower sodium concentration when compared to 0.9% sodium chloride. Studies in human patients have shown that the administration of 0.9% sodium chloride in patients prone to hyperkalemia is associated with a similar or higher serum potassium concentration than in patients treated with balanced isotonic crystalloids, and other adverse effects, such as hyperchloremic metabolic acidosis, were common (56, 57). The administration of balanced isotonic crystalloids in animals with hypoadrenocorticism or urethral obstruction has been shown to provide more rapid correction of acid-base imbalances and may prevent neurological injury secondary to rapid correction of hyponatremia, with no significant differences found in time to potassium correction compared to 0.9% sodium chloride (58–61).

None of the commercially available isotonic crystalloids contain a substantial quantity of potassium and, as a result, addition of potassium to intravenous fluids may be necessary for patients receiving longer term fluid therapy. Potassium supplementation of IV fluids can be with potassium chloride or potassium acetate additives, either with or without potassium phosphate (**Table 3**). Potassium supplementation is ideally calculated according to serum potassium level and, unless life-threatening hypokalemia is occurring, the rate should not exceed 0.5 mEq/kg/h. The existing potassium in the administered fluid is taken into consideration when calculating a rate of replacement.

Magnesium Concentration

Hypomagnesemia occurs commonly in critically ill cats and dogs and magnesium supplementation can be challenging. Plasma-Lyte and Normosol fluids contain supplemental magnesium and may be used in patients with suspected hypomagnesemia, patients considered at risk of hypomagnesemia, and patients documented to have mild hypomagnesemia. A suggested slow replacement dose for magnesium is 0.3–0.5 mEq/kg/day (62). At maintenance rates (∼3 ml/kg/h), Plasma-Lyte and

Normosol solutions would provide 0.2 mEq/kg/day of magnesium. For patients documented to have moderate to severe hypomagnesemia additional magnesium supplementation is indicated. In patients with hypermagnesemia, it is suggested to avoid magnesium containing fluids. Magnesium containing fluids are compatible with blood products (63, 64).

Calcium Concentration

Lactated Ringer's solution contains a small quantity of calcium (0.020 g/L $CaCl_2$), which is insufficient to treat a patient with hypocalcemia. It has been commonly recommended to avoid co-administration of LRS with blood products due to concerns that the calcium could be chelated by the citrate anticoagulant in the blood product, leading to loss of citrate activity and clotting of the blood product. Several studies have shown that the calcium concentration in LRS is not associated with increased coagulation of blood products, and LRS is safe to co-administer with blood transfusions (65, 66).

Acid-Base Effects of Fluids

pH of the Bag

An obvious difference between crystalloid fluid constituents and plasma is the difference in pH of the fluid itself (excluding Plasma-Lyte A). Crystalloid fluids tend to be acidic in nature. This is due the reaction of air with water and the process of heat sterilization. In addition, manufacturers often adjust the pH to a more acidic level for reasons such as improving stability and inhibition of microbial growth. The low pH of IV fluids has led to the suggestion that they can cause or worsen an acidemia. Although the pH of fluids can be low, the total quantity of acid (titratable acidity) is minimal and very readily buffered by the body. It will not significantly alter the acid-base balance of a patient (67). Plasma-Lyte A is essentially equivalent to Plasma-Lyte 148 or Normosol-R other than having a pH of 7.4. The total difference in hydrogen ion concentration between Plasma-Lyte 148 and Plasma-Lyte A is inconsequential to the body (68). An experimental study of hemorrhagic shock in pigs compared the acid base effects of Plasma-Lyte A, LRS and 0.9% sodium chloride and found no difference in the acid base balance of the animals resuscitated with Plasma-Lyte A or LRS (68).

Hyperchloremic Metabolic Acidosis

As previously discussed, the administration of chloride rich fluids (i.e., 0.9% sodium chloride) can cause hyperchloremia and a metabolic acidosis (49, 67). The delivery of high chloride filtrate to the kidney reduces renal bicarbonate reabsorption (69). The acid-base effect can also be considered in terms of the SID. Healthy dogs and cats have a SID of ∼30–40 mEq/L (depending on laboratory reference ranges). Administration of fluids with a low SID will reduce the patient's SID, promoting a metabolic acidosis, whereas high SID fluids will promote a metabolic alkalosis. Chloride rich fluids have a low (or zero in the case of 0.9% sodium chloride) SID and as such are considered acidifying fluids. Since balanced isotonic crystalloids are used more commonly than 0.9% sodium chloride in veterinary medicine, hyperchloremic metabolic acidosis is less of a concern (70). The addition of potassium chloride to IV fluids can result in hyperchloremia and monitoring chloride in animals receiving fluid therapy for any sustained period is recommended.

IV Fluids Containing Organic Anions

An ideal isotonic crystalloid would be one that matches the composition of plasma. Plasma of normal dogs and cats generally has a sodium concentration of ∼140–150 mEq/L, a chloride concentration of ∼95–110 mEq/L, and a bicarbonate concentration of ∼20 mEq/L. A crystalloid with this composition is appealing, however, bicarbonate is difficult to keep stable in solution and needs to be stored in glass. As a result, manufacturers have added organic anions to IV fluids that are stable in solution and will act as "bicarbonate precursors" or buffers. The metabolism of these substances in the body leads to the consumption of hydrogen ions (equivalent to the production of bicarbonate). Commonly used organic anions include lactate, acetate, and gluconate. Gluconate it excreted in the urine and not metabolized does not contribute to the acid base balance of the patient (71, 72).

Metabolism of organic anions such as lactate and acetate can increase plasma bicarbonate concentration in a dose dependent manner and can promote the development of a metabolic alkalosis (49, 71). The acid-base effect of organic anions can also be reflected by the fluid SID. Balanced crystalloids have an SID that is similar or higher than that of normal plasma (see **Table 1**) and will help to normalize SID in patients with a metabolic acidosis.

Lactate

Rapid administration of large volumes of lactate (L-lactate or a mixture of L and D-lactate) containing fluids can cause elevations in blood lactate. As lactate monitors used in clinical medicine only read L-lactate, the impact of lactate administration will be more evident with fluids containing higher levels of L-lactate. Healthy dogs receiving 180 ml/kg of LRS over an hour had a significant increase in blood lactate which was resolved 60 min after the end of the infusion (73). The increase in blood lactate following administration of lactate containing fluids is of a greater magnitude and persists for longer in hemodynamically unstable animals. Experimental studies exist comparing the administration of LRS vs. lactate free fluids in models of hemorrhagic shock (74, 75). The animals receiving LRS had a significant increase in blood lactate concentration following fluid resuscitation compared to the non-LRS animals. This was not associated with an acidosis because the lactate contained in IV fluids is a salt (sodium lactate) rather than lactic acid. This iatrogenic elevation of blood lactate can confuse the assessment of hemodynamic status.

The metabolism of lactate occurs primarily in the liver. Animals with significant hepatic dysfunction, such as hepatic failure or portosystemic shunt, may have limited lactate metabolism, resulting in elevations of blood lactate and lack of buffering capacity. For this reason, it is generally recommended to avoid lactate containing fluids in patients with liver dysfunction. Unlike lactate, acetate is readily metabolized by extra-hepatic tissues such as skeletal muscle and can be utilized by patients with hepatic dysfunction.

The infusion of lactate has been reported to have systemic effects including immune, coagulation and hemodynamic changes. Although there are a growing number of comparison studies between lactate and acetate containing fluids, the results are inconsistent, and more research is needed to fully understand these issues (76).

Dilutional Acidosis

A well-cited acid-base abnormality associated with fluid administration is a dilutional acidosis. Dilutional acidosis is the result of extracellular fluid volume expansion with a non-bicarbonate containing fluid (77). As a result, there is the same quantity of bicarbonate in a larger volume, leading to a fall in bicarbonate concentration. It has been most frequently associated with rapid infusions of large volumes of 0.9% sodium chloride. But it will occur with the infusion of any non-bicarbonate containing fluid such as LRS or Plasma-Lyte 148. This was demonstrated by a study in human cardiopulmonary bypass patients where they compared the use of Plasma-Lyte 148 with a buffer free fluid like 0.9% sodium chloride for initial pump prime (78). After 2 min of full pump flow both groups of patients had developed a similar degree of metabolic acidosis (dilutional acidosis), compared to baseline. Although at the end of the procedure the group that received Plasma-Lyte 148 had resolved their metabolic acidosis while the group with non-buffered fluids had a residual metabolic acidosis. The organic anions in balanced crystalloids help resolve the dilutional acidosis more rapidly, while patients receiving 0.9% sodium chloride take longer to resolve the acidosis. It is important to note that dilutional acidosis only occurs after rapid administration of exceptionally large volumes of fluids.

Fluid Osmolality

Osmolality is a measure of the total concentration of solute (number of particles) in a quantity of solvent (number of osmoles/kg solution) and osmolarity is the number of osmoles/L of solution. In most clinical scenarios the mOsm/L is equivalent to the mOsm/kg, and the terms are considered interchangeable (79). When predicting the solute concentration of a solution through calculations adding together concentrations of known osmoles, it is the mOsm/L (osmolarity) that is being determined, whereas measured values (determined by freezing point depression) are reported as mOsm/kg (osmolality). This has some relevance to IV fluid solutions as the theoretical osmolarity tends to overestimate the measured osmolality because molecules do not always fully dissociate under physiologic conditions. For example 0.9% sodium chloride has a calculated osmolarity of 308 mOsm/L but the measured osmolality is 286 mOsm/kg (80).

The osmolality of an IV fluid can affect cells at the site of infusion before the fluid is diluted by the blood volume. Hyperosmolar fluids are of particular concern although very hypoosmolar fluids, such as sterile water, can also create injury. Peripheral vessels are small, and infused fluids have contact with endothelial cells in addition to erythrocytes. To avoid phlebitis, infusion of hyperosmolar fluids through a central vessel, where flow rates are faster, and the infused fluid is less likely to contact the vessel wall, is recommended. Studies suggest that a fluid osmolality >600 mOsm/L is too high for peripheral infusion (81, 82). A study of infusion of a parenteral nutrition solution with an osmolality of 840 mOsm/L via a peripheral vein in experimental dogs reported a high rate of thrombophlebitis at 36 h, which further supports this recommendation (83).

Galactomannan

Plasma-Lyte 148 contains sodium gluconate that is produced from fermentation by Aspergillus sp., and it has been shown that the fluid can be contaminated by small quantities of galactomannan. Galactomannan is a component of the cell wall of Aspergillus, and galactomannan assays are used as diagnostic tests to identify aspergillus. The presence of Plasma-Lyte 148 in a diagnostic sample can cause a false positive result (84).

Fluids for Medication Delivery

Any crystalloid can be used as a carrier or diluent for medications, and carrier fluids are typically either D5W or 0.9% sodium chloride, since these are not complex, are acidic, and are less likely to alter the medication it is carrying. The prescribing information of the individual drug to be infused will indicate which crystalloid carrier solution can be used. Balanced isotonic crystalloids can be co-administered with many medications, but some important drug incompatibilities have been identified. For example, Plasma-Lyte 148 is incompatible with pantoprazole, cyclosporine, and midazolam while LRS is incompatible with diazepam, ketamine, and cyclosporine (63, 85).

Summary

The ideal balanced isotonic solutions will vary according to species. For most small animal patients, the traditionally coined "balanced" isotonic crystalloids are appropriate for fluid resuscitation, rehydration, and maintenance fluid support. In critically ill animals or patients with electrolyte or acid-base abnormalities and/or with hepatic disease, fluid choice should be based on the patient's existing acid/base and electrolyte condition, in consideration of the available information. Animals with extreme electrolyte imbalances should have a fluid prescription that corrects those imbalances without causing additional complications. Animals receiving high volumes of fluid therapy or several days of fluid therapy should be monitored for electrolyte and acid-base changes that could require a change in the fluid prescription. Hypoproteinemic animals may also benefit from infusion of a colloid solution.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the research and writing of this manuscript.

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REVIEW
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Colloids Yes or No? - a "Gretchen Question" Answered

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Colloid solutions, both natural and synthetic, had been widely accepted as having superior volume expanding effects than crystalloids. Synthetic colloid solutions were previously considered at least as effective as natural colloids, as well as being cheaper and easily available. As a result, synthetic colloids (and HES in particular) were the preferred resuscitation fluid in many countries. In the past decade, several cascading events have called into question their efficacy and revealed their harmful effects. In 2013, the medicines authorities placed substantial restrictions on HES administration in people which has resulted in an overall decrease in their use. Whether natural colloids (such as albumin-containing solutions) should replace synthetic colloids remains inconclusive based on the current evidence. Albumin seems to be safer than synthetic colloids in people, but clear evidence of a positive effect on survival is still lacking. Furthermore, species-specific albumin is not widely available, while xenotransfusions with human serum albumin have known side effects. Veterinary data on the safety and efficacy of synthetic and natural colloids is limited to mostly retrospective evaluations or experimental studies with small numbers of patients (mainly dogs). Large, prospective, randomized, long-term outcome-oriented studies are lacking. This review focuses on advantages and disadvantages of synthetic and natural colloids in veterinary medicine. Adopting human guidelines is weighed against the particularities of our specific patient populations, including the risk–benefit ratio and lack of alternatives available in human medicine.

Keywords: albumin, dextran, gelatin, HBOC, hydroxyethyl starch, fresh frozen plasma, fluid therapy

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BACKGROUND

A colloid is the collective term for electrolyte solutions containing macromolecules, a portion of which cannot pass freely out of the healthy intravascular space. Hence, they exert a colloid osmotic pressure (COP) and thereby retain or attract water commensurate with the number rather than the size of the colloid molecules on each side of the microvascular barrier (1). Natural colloids include blood products and albumin solutions, such as human serum albumin (HSA) and canine serum albumin (CSA). Synthetic colloids include hydroxyethyl starches (HES), gelatins, and dextrans (2) (**Table 1**). Synthetic colloids and particularly HES solutions have been preferred as volume expanders over isotonic crystalloids for decades (3). This was based on their presumed "volume-sparing effect." Indeed, it was accepted that less colloid than isotonic crystalloid is necessary to reach adequate volume expansion in various populations of patients. Furthermore, since synthetic colloids do not readily cross the vascular barrier and produce COP, they were believed to contribute

TABLE 1 | Synthetic and natural colloids and their physicochemical characteristics.

Colloid	Colloid Source	Concentration	Carrier solution	Mean MW (kDa)/MS/C2/C6 ratio	*In vitro* COP (mmHg)
Plasma	Plasma (dog/cat)	25to 30 g/L	n/a	n/a	17
HSA 5%	Pooled human plasma	50 g/L	Sterile water	∼66 kDa	20
HSA 20%, 25%	Pooled human plasma	200–250 g/L	Sterile water	∼66 kDa	> 200
CSA¶ (5% /16%)	Pooled canine plasma	50/166 g/L	0.9% saline	∼60 kDa	n/a
HES, tetrastarch (6% Voluven*)	Waxy-maize starch	60 g/L	0.9 saline	130/0.4, 9:1	36
HES, tetrastarch (6% Volulyte*)	Waxy-maize starch	60 g/L	Buffered, polyionic	130/0.4, 9:1	36
HES, tetrastarch (Venofundin†)	Potato starch	60 g/L	0.9% saline	130/0.42, 6:1	36
HES, tetrastarch (Tetraspan†)	Potato starch	60 g/L	Buffered, polyionic	130/0.42, 6:1	36
HES, hetastarch (Hespan†)	Waxy-maize starch	60 g/L	0.9% saline	600/0.75	33
HES, hetastarch (Hextend†)	Waxy-maize starch	60 g/L	Buffered, polyionic	600/0.75	33
HES, pentastarch (HAES-steril*)	Waxy-maize starch	60 g/L	0.9% saline	200/0.5, 5:1	30–35
HES, pentastarch (HyperHAES*)	Waxy-maize starch	60 g/L	7.5% saline	200/0.5, 5:1	30–35
Gelatin (Gelofusine 4%†)	Bovine collagen	40 g/L	0.9% saline	∼30 kDa	33
Gelatin (Gelafundin-Iso†)	Bovine collagen	40 g/L	Buffered polyionic	∼ 30 kDa	33
10% dextran-40 (Rheomacrodex)	sucrose	100 g/L	0.9% saline	40 kDa	n/a
6% dextran-70 (Macrodex§)	sucrose	60 g/L	0.9% saline	70 kDa	62
6% dextran-70 (RescueFlow)	sucrose	60 g/L	7.5% saline	70 kDa	n/a
HBOC (Oxapex)	Bovine hemoglobin	60–70 g/L		65	19

HBOC, Hemoglobin-based oxygen carrier; HSA, human serum albumin; CSA, canine serum albumin; HES, hydroxyethyl starch; Trade names in brackets, MW, molecular weight; MS, molar substitution; kDa, kilo Dalton; COP, colloid osmotic pressure.
**Fresenius Kabi AG, Switzerland. †B. Braun Melsungen AG, Germany; §Meda, Sweden; ¶HemoSolutions, LLC, Colorado Springs. Names and manufactures for the listed colloids are examples and vary between different countries.*

to prevention and reduction of edema formation (2, 4). However, the advantages of synthetic colloids have been questioned in recent years for two main reasons. First, regardless of their proposed short-term benefits, synthetic colloids are now known to be associated with serious long-term adverse effects. Second, the microanatomic and physiological basis of transvascular fluid flux has been revised in light of the more widespread appreciation of the role played by the endothelial surface layer (ESL) (see below). This newer understanding has raised doubts regarding the fundamental validity of the physiological basis for colloid therapy. Nevertheless, according to an international survey from 2016, synthetic colloids and particularly HES were extensively used in small animals (5). Since 2013 pharmacovigilance authorities worldwide have restricted the use of HES in people and colloid usage has therefore shifted to other products (namely, albumin and gelatins) (6). As a result, veterinarians are facing difficulties in procurement and overall reduction in availability of HES. Whether a similar shift toward alternative colloids is possible and safe for veterinary patients is unclear. This review will describe the characteristics and adverse effects of various synthetic and natural colloids, with the aim to provide risk-assessment and evidence-based recommendations for their use.

Abbreviations: AKI, acute kidney injury; COP, colloid osmotic pressure; CRI, constant rate infusion; CSA, canine serum albumin; EG, endothelial glycocalyx; ESL, endothelial surface layer; FFP, fresh frozen plasma; Hb, hemoglobin: HBOC, hemoglobin-based oxygen carrier; HES, hydroxyethyl starch; HSA, human serum albumin; EU, European Union; HES, hydroxyethyl starch; HSA, human serum albumin solutions; kDa, kilodalton; pRBC, packed red blood cell; RCT, randomized clinical trial; RRT, renal replacement therapy.

PHYSIOLOGY OF COLLOID SOLUTIONS

Classical vs. Revised Starling Principle

According to the traditional Starling principle, the opposing hydrostatic and colloid osmotic pressures of the intravascular space and the interstitium dictate transvascular fluid fluxes. Thus, administering a fluid that is preferentially retained in the intravascular space and with a COP higher than that of a crystalloid will expand intravascular volume to a greater extent per unit volume administered (1). However, the Starling principle has been revised in recent decades.

The newer "revised" or "extended" Starling principle considers the role of the endothelial glycocalyx (EG) within the ESL as an additional barrier to fluid movement across the vascular wall (7). The EG is a meshwork of membrane-bound complex sugars lining the luminal surface of the endothelium of all mammalian vessels (7). As part of the ESL, it acts as a selective barrier to movement of molecules across the vascular wall, due to its tight entanglement and predominantly negatively charged structure (8). The EG retains albumin and other proteins within the intravascular space. In that way, it is a major determinant

of vascular permeability to fluid (9). The EG maintains a relatively low rate of filtration throughout the entire capillary length. At normal hydrostatic pressures, no reabsorption from the interstitium into the intravascular space occurs in non-fenestrated capillaries (10). Contrary to the "classical" Starling principle, the revised Starling principle proposes that the opposing pressures determining fluid extravasation or retention are the capillary hydrostatic pressure, the capillary COP (including that of the EG), and the hydrostatic and colloid osmotic pressure of the sub-glycocalyx area, which is virtually protein free (10). Therefore, in scenarios where the EG is intact, the major determinant of fluid filtration is the capillary hydrostatic pressure. However, in situations where the EG becomes damaged, such as systemic inflammatory states, it can no longer maintain its barrier function and extravasation of both plasma proteins and electrolytes, or administered colloids and crystalloids, is equally likely (11). Furthermore, extravasated colloid solutions increase the interstitial COP, thus retaining more fluid and aggravating interstitial edema (12). Therefore, theoretically, the change in intravascular volume that is achieved from a given dose of crystalloid or colloid depends on the integrity of the individual's EG. It is noteworthy that most of the statements supporting the revised Starling principle are derived from the experimental setting, and the clinical importance of changes in the EG requires determination. Indeed, the clinical significance of some aspects of the revised Starling principle has been called into question in a recent review (13). The interested reader is referred to the article "Advances in the Starling principle and microvascular fluid exchange; consequences and implications for fluid therapy" of this special issue for a more in-depth review on the EG.

Volume Effects of Colloids

Classically, colloids were believed to exert three to four times the volume effects of crystalloids (14, 15). This has been demonstrated in patients without systemic disease (16), in older studies of people in shock (17, 18), and in experimental hemorrhagic shock models (19–23). Several recent clinical studies, however, failed to corroborate these findings in systemically ill people, suggesting colloid-to-crystalloid relative volume expansion ratios of 1:1–1:1.5 (24). The proposed cause for this discrepancy is the damage to the EG resulting in fluid extravasation of both crystalloids and colloids, and therefore similar volume effects (2). In states of volume depletion, however, colloids seemingly exert a superior volume expanding effect to crystalloids. In people undergoing planned normovolemic hemodilution to a hematocrit of 21%, replacement of the removed blood with 115% volume of 6% HES 130/0.4 restored intravascular volume to 105 ± 4% (25). In a similar setting, replacement of four times the removed blood volume with Ringer's lactate solution led to a volume effect of only 17 ± 10%. In contrast, subsequent infusion of a 20% albumin solution to correct a volume deficit led to a volume effect of 184 ± 63% (16). Several experimental hyper- and normovolemic hemodilution models have shown similar findings, whether by evaluating volume expansion or using resuscitation endpoints (26–28).

Interestingly, these findings contrast with the revised Starling principle, whereby in the transient state of decreased hydrostatic pressure, both crystalloids and colloids should be able to equally restore blood volume (10). The cause for these discrepant findings is probably multifactorial. For instance, they might simply be the result of incomparable study designs or imprecise or different methodology. Indeed, the current techniques for estimating blood volume (such as dilution tracer techniques and the more common measurement of hemodilution) are challenging to perform and may carry inherent errors (12, 13, 29, 30). As a result, comparison between studies is difficult. This further hinders the ability of scientific evidence to translate into meaningful clinical guidelines.

In addition to "superior" volume expansion effects, colloids are proposed to stay "longer in the vessel" than crystalloids. While crystalloids are expected to redistribute over 20–40 min, studies have shown that the colloids persist in the intravascular space for 2–3 h in healthy euvolemic volunteers (31–33). Systemic inflammatory and otherwise "leaky" states are expected to shorten the duration of this effect (34, 35). However, extensive studies on redistribution of colloids are lacking (12). Further, colloids (and especially HES) have been specifically indicated in states of increased capillary permeability to "plug the holes in the endothelium." The ability of the macromolecules contained in colloids to wedge into endothelial intercellular orifices, a product of systemic inflammation and endothelial dysfunction, has been proclaimed in textbook chapters and review articles (4, 14). This has been extrapolated mostly from experimental models using entire animals (36–42), isolated tissues (43), or endothelial cell lines (44). However, this ability remains to be tested in the clinical setting. Whether colloids reduce or exacerbate fluid extravasation in systemic inflammatory states remains controversial with studies reporting opposing results (34, 45–47). The reader is reminded that evaluating extravasation is challenging in the clinical setting, which might be a plausible explanation for these discrepancies. Another explanation for the "plugging potential" of colloids may lie in their interaction with the EG. Indeed, experimental studies have demonstrated that albumin might exert protective effects on the EG (48–52). In the same series of experiments, HES showed a similar, albeit weaker, protective effect (53). This is proposed to be the result of colloids binding to the glycosaminoglycan side chains of proteoglycans and glycoproteins and stabilizing the scaffolding structure of the EG (54, 55). However, in the majority of those studies, the study fluid was infused before an insult on the EG. Therefore, infusing colloids once the EG damage has occurred might not carry the same protective effect.

Colloid Osmotic Pressure Optimization

Synthetic colloids have been used as a substitute for albumin in patients with hypoalbuminemia with the rationale that they are capable of restoring plasma COP. Indeed, several veterinary studies in hypoalbuminemic patients have demonstrated that HES stabilizes (56) or increases plasma COP (57–59), with one study demonstrating a subjective decrease in peripheral edema when using high molecular weight HES (hetastarch) (60). However, the decrease in edema was not correlated with the dose

administered and a drop of COP was noted after subsequent HES administrations. In another study where COP increased after administration of HES, it returned to baseline within 12 h of administration (58).

Administering synthetic colloids as a constant rate infusion (CRI) seems to be unique to veterinary medicine. Veterinarians often use synthetic colloids as CRIs for patients with hypoalbuminemia and edema (5). Non–peer-reviewed conference proceedings (61, 62) and review articles (2) recommend doses of 1–2 ml/kg/h or the maximal recommended daily dose divided by 24 h to support patients with low albumin or COP, respectively. In a recent study, HES 130/0.4 was able to maintain COP levels but did not significantly increase COP when administered as a CRI over 24 h to a small group of dogs with hypoalbuminemia (56). To the authors' knowledge, there are no other publications reporting the efficacy of administering colloids as a CRI rather than as a bolus. Ultimately, whether normalizing and maintaining COP should be a critical point in patient care is unclear as extravasation is at least as dependent on the integrity of the EG as it is on intravascular COP. Furthermore, synthetic colloids are not capable of carrying out all the other roles of natural colloids and specifically albumin. Therefore, they cannot be used interchangeably in the hypoalbuminemic patient.

Summary on Physiology of Colloid Solutions

In conclusion, natural and synthetic colloids may exert greater intravascular volume expanding effect per unit administered than crystalloids in healthy patients or patients with hypovolemia. However, caution is required when administered in patients with EG damage or other causes of increased vascular permeability. Not only does increased vascular permeability reduce the expansion of volume that colloids can lead to but extravasation of the macromolecules might exacerbate edema and subsequently impair tissue oxygenation. Previous indications for use of colloids include volume expansion (including perioperative hypotension) and COP optimization. These indications should be revised considering specific conditions (e.g., intact or damaged EG), alternative therapies (e.g., vasopressors rather than fluids for drug-induced hypotension), potential harmful effects (e.g., HSA leads to anaphylactic reactions in dogs), and overall availability (e.g., canine albumin found only in limited numbers of countries).

HYDROXYETHYL STARCH

Characteristics of HES Solutions

Hydroxyethyl starch is a potato or waxy maize–derived amylopectin, modified by the substitution of hydroxyl groups with hydroxyethyl residues on the glucose subunits to increase resistance to degradation in the blood. Recent reviews described pharmacokinetics, pharmacodynamics, effects, and adverse effects of HES (2, 4, 63, 64). Preparations are characterized by the mean molecular weight (molecular size, indicated in kilodalton, kDa), molar substitution (mole of hydroxyethyl residues per mole of glucose subunit), C2:C6 ratio (locations of hydroxyethyl residues on the carbon atom of the glucose subunits) and the concentration [e.g., 6% (60 g/L) vs. 10% (100 g/L)], the carrier solution (normal saline vs. polyionic, buffered, and balanced), and the starch source [potato (e.g., HES 130/0.42) vs. maize starch (e.g., HES 130/0.4)].

Since its introduction on the market in the 1970s, HES was one of the most commonly used resuscitation fluids in people worldwide (2, 3).

Mechanisms of Adverse Effects of HES

HES-associated adverse effects, such as nephrotoxicity, coagulopathy, tissue storage, and therapy-resistant pruritus, were reported early after its introduction on the market (2). After intravenous administration, large HES molecules (>60 kDa) are degraded by plasma α-amylase and by the reticuloendothelial system, before they undergo glomerular filtration and urinary excretion (2). However, HES is also rapidly (within hours) taken up by a wide variety of tissues in the body, with skin and kidney being the most affected organs (65). Intracellular HES degradation is slow and incomplete, and HES deposits persist up to 10 years in the human kidney (65). A key mechanism responsible for HES-induced acute kidney injury (AKI) is osmotic nephrosis after HES uptake in renal proximal tubular epithelial cells by pinocytosis. Osmotic nephrosis is characterized histologically by a vacuolization (i.e., storage in lysosomes) and swelling of the renal tubular epithelial cells, which compromises and occludes the tubular lumen, with subsequent stasis of urine flow (66). Another mechanism is hyperviscosity-mediated injury, in which hyperoncotic tubular fluid leads to stasis of flow and obstruction of the tubular lumen (**Figure 1**) which has been described with 10% HES solutions (ovine endotoxemic shock model) (67). Further, renal interstitial cell proliferation, macrophage infiltration, and tubular damage are documented pathological mechanisms of HES-induced adverse effects on renal function (68, 69). In an isolated renal perfusion model, 10% HES 200/0.5 caused more tubular damage compared with 6% HES 130/0.42 and Ringer's lactate (68).

Mechanisms for HES-induced coagulopathy include dilution of clotting factors, impaired platelet function, decreased concentrations of circulating von Willebrand factor and factor VIII, impaired factor XIII–fibrin cross-linking, and enhanced fibrinolysis, with the subsequent risk of bleeding complications (2, 4, 70, 71). The pathophysiologic consequence is an impairment of different hemostatic variables (i.e., activated partial thromboplastin time) (71), which may also complicate the interpretation of coagulation abnormalities in critically ill human and animal patients (e.g., HES induced vs. disseminated intravascular coagulation-induced prolongation of clotting times).

Adverse Effects of HES in Humans

Acute Kidney Injury and Mortality

The presumed beneficial effects of HES and the development of modern and putatively safer HES preparations seemed to outweigh the described adverse effects for a long time. This changed after the results of large multicenter randomized controlled trials (RCTs) in people, which compared HES and crystalloids for resuscitation of critically ill patients. Indeed,

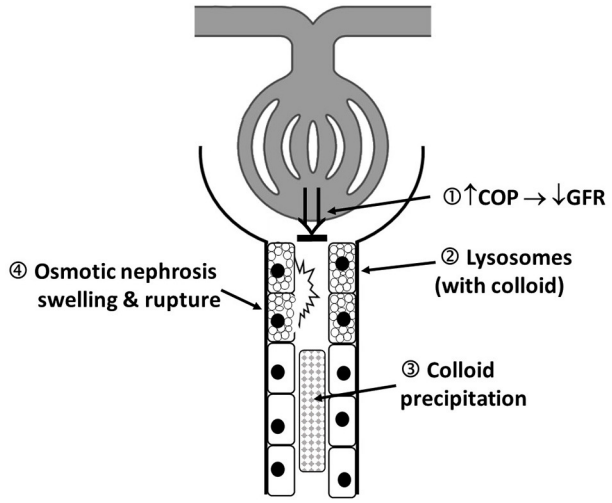

FIGURE 1 | Schematic illustration of proposed mechanism of colloid-induced AKI: 1. Colloid induced increase in plasma COP that decreases filtration pressure and consequently GFR ("hyperoncotic AKI"). 2. Accumulation of colloid containing proximal tubular lysosomes, leading cellular dysfunction. 3. Local hyperviscosity and colloid precipitation, forming of occluding casts. 4. Osmotic nephrosis represents vacuolization and swelling of the renal proximal tubular cells; It can be reversible, and function restored but may also be a first step in the development of irreversible cell lesions. The above mechanisms are not mutually exclusive and may occur in combination. AKI, acute kidney injury; COP, colloid osmotic pressure; GFR, glomerular filtration rate.

three large influential RCTs in nearly 600 patients with severe sepsis ("VISEP" in 2009), in 800 patients with severe sepsis with high illness severity ("6S" in 2012), and in 7,000 less sick intensive care patients ("CHEST" in 2012) found an increased risk of AKI and renal replacement therapy (RRT) (in all three trials), and mortality (only in "6S") in patients receiving HES (72–74) (**Supplementary Table 1**). These findings challenged the risk:benefit ratio of HES. Proponents criticized these landmark trials for their "flawed" design, i.e., late use of HES in patients who were already volume resuscitated (in VISEP study patients received HES for up to 21 days) and including patients who received HES even though they were in renal failure (75). Around the same time, two smaller RCTs in 115 patients with penetrating and blunt trauma ("FIRST" in 2011) and in 156 patients with severe sepsis ("CRYSTMAS" in 2012) reported no adverse effects (76, 77). In addition, a large open-label randomized comparison between crystalloids and various colloids for the treatment of acute hypovolemia in nearly 2,900 patients with hypovolemic shock ("CRISTAL" in 2013) showed no significant difference in 28-days mortality, but a significant reduction in mortality at 90 days [34.2% (crystalloids) vs. 30.7% (colloids), $p = 0.03$] in the colloid group (70% of colloids were HES), and more vasopressor-free and ventilator-free days by day 28. The study also found no evidence that colloids increased the risk of AKI or any other serious adverse event (**Supplementary Table 1**) (78). Independently of these controversial RCT results, almost 90 HES-related scientific articles authored by a prominent German anesthetist and prolific defender of HES were retracted 2012 for data fabrication and lack of ethics approval (79, 80). The retraction of such a large body of work has had far-reaching effects on clinical practice and research oversight (81). Because of the RCTs demonstrating harm in critically ill patients receiving HES and the retraction of the HES-supporting scientific articles, several systematic reviews then highlighted the adverse effects of HES (82–85). As a consequence, two pharmacovigilance safety reviews of HES worldwide in 2012/2013 and in the European Union (EU) in 2017/2018 led to progressive restrictions of HES use in people (86). Since then, experts worldwide have considered HES solutions to be contraindicated in patients with sepsis or other critical illnesses, additional warnings on packaging are required in the EU, and supply has been limited to accredited hospitals after training of healthcare professionals (86). These restrictions are still a matter of debate between HES proponents and opponents. Nevertheless, between 2007 and 2014, the proportion of patients receiving colloids in human medicine decreased significantly, which was primarily due to a decrease in the use of HES, despite an overall increase in the use of human albumin (6). As most of the negative effects of HES reported in the RCTs involved patients with sepsis, in 2013 European medicines authorities requested further studies evaluating the safety and efficacy of HES in perioperative non-septic patients (86). Several smaller studies and RCTs in non-septic patients in the perioperative setting found no evidence of a nephrotoxic effect of HES (87, 88). Likewise, two recent larger, multicenter trials in 4,545 ("RaFTinG" in 2018) and 775 ("FLASH" in 2020) surgical patients also found no significant difference in mortality between patients who received HES or crystalloids and AKI in one (89), and according to the authors a reduced risk of RRT and AKI in another (90) (**Supplementary Table 1**). Notably, "RaFTinG" was criticized for statistical over-adjustment and "FLASH" for misrepresenting results (91, 92). In summary (and regardless of the exhaustive criticism all RCTs have been subjected to), critically ill and specifically septic patients seem to be particularly burdened by the nephrotoxicity of HES. This is exacerbated by long-term HES administration to otherwise hemodynamically stable patients. Such effects seem to be lost in less severely ill patients and specifically those presented with acute hypovolemia or those requiring perioperative fluid therapy.

HES Coagulopathy

In addition to the results regarding kidney failure in the aforementioned studies, HES-induced coagulopathy and hemorrhage is also a well-known adverse effect (73, 74). Despite improved physicochemical properties of newer HES products (e.g., tetrastarch), a systematic review from 2011 found HES 130/0.4 led to hypocoagulability in a dose-dependent fashion (70). This was supported in further clinical studies, where patients who received HES lost more blood and had higher need for packed red blood cell (pRBC) transfusions than patients receiving only crystalloids (74, 88). In 6S, more patients in the HES group than in the Ringer's acetate group received blood products, including packed red cells (relative risk, 1.28; 95% CI 1.12–1.47; $p < 0.001$) (74). In two recently published RCTs, HES therapy was associated with a blood loss more than twice as high as with crystalloid alone (87, 93). In contrast, a meta-analysis

including 49 studies in a total of nearly 3,439 patients undergoing cardiac surgery (i.e., colloids are used as priming solution and volume replacement) could not identify evidence for a higher risk of bleeding, blood transfusion, or reoperation associated with tetrastarch compared with pentastarch, albumin, gelatin, and crystalloids. Tetrastarch was superior to human albumin in terms of blood loss and transfusion requirements (blood loss after tetrastarch vs. albumin: standardized mean difference, −0.34; 95% CI, −0.63 to −0.05; $p = 0.02$) (94).

Safety Recommendation in People

According to the latest recommendation from the European Medicines Agency from 2018, valid for the EU countries, HES use should be limited to initial volume resuscitation with a dose not exceeding 30 ml/kg over a period of administration not exceeding 24 h, and that kidney function should be monitored for at least 90 days thereafter. In addition, HES is contraindicated in sepsis, critically illness, burns, severe preexisting coagulopathy, and bleeding in people, among others (86).

Adverse Effects of HES in Small Animals

HES is currently the most used and studied synthetic colloid in veterinary medicine. Guidelines or absolute contraindications on the use of HES do not yet exist for small animals. Longstanding recommendations for the use of HES in animals have been mostly extrapolated from human medicine so the recent changes in human guidelines have led to more veterinary research.

HES-Induced Acute Kidney Injury in Small Animals

Most of the studies of the renal effects of HES in dogs and cats have been retrospective or experimental and have yielded conflicting results (95–102) (**Table 2**). In one retrospective study, treatment with 10% HES 200/0.5 was a risk factor for adverse outcome, including in-hospital death or AKI, and the risk of AKI increased with increasing HES dose (97). In four retrospective studies in critically ill dogs and cats, 6% HES 130/0.4 was not associated with an increased risk for AKI (98–101), although the number of HES days was significantly associated with an increase in AKI grade within 10 days post-HES (98). Two of these studies specifically evaluated a subgroup of cats and dogs with sepsis and found no HES-associated acute kidney injury (100, 101). Interpretation of these studies is hampered by the fact that different HES types are used, the definition of AKI is not standardized, study populations are comparatively small, and the studies are retrospective in nature, indicating associations rather than causality. Further, creatinine has a poor sensitivity to detect early stages of AKI. A conclusion regarding the renal safety of tetrastarch based on these four studies is therefore limited.

Two experimental studies compared the effect of 6% HES 130/0.4 (bolus of ∼20 ml/kg once), of other colloids, and of crystalloids on kidney injury in canine hemorrhagic shock models (95, 96). Concentrations of several plasmatic and urinary renal biomarkers were analyzed, e.g., neutrophil gelatinase-associated lipocalin, a protein expressed after renal proximal tubular damage and secreted in blood and urine. Both studies found no association between HES and biomarkers of AKI within 3 or 72 h after HES bolus, respectively (95, 96). It is unclear to what extent these results can be extrapolated to critically ill or septic dogs and cats, as acute hemorrhagic shock was induced in previous healthy dogs, and the studies were conducted over a relatively short period of time in a small group of dogs and in a defined disease model.

Prospective RCTs are needed and are currently underway. Recently, results from a randomized, blinded, clinical trial to compare different urine biomarkers (e.g., neutrophil gelatinase-associated lipocalin) of AKI in dogs receiving 6% HES 130/0.4 vs. Hartmann's solution for shock resuscitation were published (102). No differences in urinary AKI biomarkers between the HES group (21 dogs) and the crystalloid group (19 dogs) were found up to 24 h after the first fluid bolus. In addition, in the five dogs which developed AKI (i.e., three in the HES group, two in the crystalloid group), no significant difference in maximum Veterinary Acute Kidney Injury scores was found (102).

Intrarenal HES accumulation has also been evaluated histologically in dogs (95, 103). Tubular injury scores (based on damaged epithelial cells and presence of sloughed cells within tubular lumen) and the degree of renal tubular microvesiculation (vesicles within renal epithelial cells) were not significantly different between dogs receiving 6% HES 130/0.4 compared with dogs receiving whole blood or isotonic crystalloids in an experimental hemorrhagic shock model (95). In contrast, retrospective histopathological examination of kidney tissue from critically ill dogs revealed that the cumulative dose of 6% HES 670/0.75 was positively associated with the severity of renal tubular vacuolization (103). It is worth mentioning that osmotic nephrosis is not specific to HES administration but can be due to other drugs (e.g., mannitol, glucose, intravenous immunoglobulins), primary renal diseases, and postmortem autolysis (66). Immunohistochemical evaluation with specific HES antibodies would be ideal to provide a reliable diagnosis of HES-induced osmotic nephrosis.

HES-Induced Coagulopathy in Small Animals

Several *in vitro* and *in vivo* studies in healthy dogs and cats (104–108) have shown a dose-dependent and transient coagulation impairment after *in vitro* dilution of blood or IV administration of HES. Hemostasis assessment was performed predominately by whole blood platelet function analyses and viscoelastometric coagulation analyses (e.g., rotational thromboelastometry). Platelet function, speed of clot formation, and clot firmness were more impaired after HES than after crystalloids using similar dilutions (104–108). However, when clinical doses of HES and isotonic crystalloid (i.e., 10 ml/kg HES vs. the 3- to 4-fold volume of crystalloid) were compared *in vitro* (blood from healthy dogs) (107) or *in vivo* (experimentally induced canine hemorrhagic shock model), no difference was found (109, 110). Different results were obtained in two other studies which used thromboelastometry. In one hemorrhagic shock model, the administration of 20 ml/kg of 6% HES 130/0.4 was associated with hypocoagulability beyond effects of hemodilution (i.e., 80 ml/kg crystalloids) (111). Likewise, in critically ill dogs with spontaneous hemoperitoneum, more impaired coagulation was found after 10 ml/kg of 6% HES 130/0.4 compared with a 3-fold volume of crystalloid (112). However, in this study,

TABLE 2 | Clinical studies evaluating kidney injury after HES administration in dogs and cats (sorted by publication year).

First author (year, [reference])	Design	Species	HES type	Definition of AKI	Measurement time points	Doses	Outcome
Hayes et al. (97)	Retrospective, critically ill	Dogs (HES $n = 180$; CRYS $n = 242$)	10% HES 200/0.5	>2× increase in admission creatinine concentration or oliguria/ anuria of <0.5 mL/kg/h for >12 h	Blood creatinine concentrations at admission and during hospitalization.	Median bolus dose: 8.2 ml/kg/d (IQR 5.0–11.3 ml/kg/d); CRI median dose: 26 ml/kg/d (IQR 24.0–48 ml/kg/d)	HES increased risk of an adverse outcome including death or AKI (OR = 1.98, 95% CI = 1.22–3.22, $P = 0.005$)
Yozova et al. (100)	Retrospective, critically ill	Dogs (HES $n = 86$; CRYS $n = 115$)	6% HES 130/0.4	VAKI staging system	Plasma creatinine concentrations at admission (T0), and 2–13 days (T1), and 2–12 weeks (T2)	Median total dose: 86 ml/kg (range, 12–336 ml/kg); Median bolus 25 ml/kg/d (range, 12–62 ml/kg/d); median duration of administration 3.7 days (range, 1–9 d)	Compared to CRYS, HES did not result in greater increase in creatinine in critically ill dogs and in the subgroup of dogs with sepsis
Yozova et al. (101)	Retrospective, critically ill	Cats (HES $n = 31$; CRYS $n = 62$)	6% HES 130/0.4	IRIS AKI grading criteria and VAKI staging system	Plasma creatinine concentrations at admission (T0) and the maximum concentration measured at any time between 24 h after admission and discharge or death (T1max)	Median total dose: 94 ml/kg (range 26–422 ml/kg); median daily dose: 24 ml/kg/day (range 16–42) 3.7 days of administration (range 1–13d)	Compared with CRYS, HES did not result in greater increase in creatinine in critically ill cats and in the subgroup of cats with sepsis
Sigrist et al., (98)	Retrospective, critically ill	Dogs (HES $n = 94$; CRYS $n = 90$)	6% HES 130/0.4	IRIS AKI grading criteria	Serum creatinine concentration was recorded each available day until day 90	Median total dose: 69.4 ml/kg (range, 2–429 ml/kg); median daily dose 20.7 ml/kg/d (range, 2–87 ml/kg/d); median duration of administration 4 days (range, 1–16 d)	Compared with CRYS, HES did not result in greater increase in creatinine. Number of HES days was significantly associated with risk of increased AKI grade within 10 days post-HES administration
Sigrist et al. (99)	Retrospective, critically ill	Cats (HES $n = 26$; CRYS $n = 36$)	6% HES 130/0.4	VAKI staging system	% change from baseline to the last and highest creatinine within 2–10 days and from baseline to the last creatinine within 11–90 days	Mean total dose: 98.5 ml/kg (range, 8–278 ml/kg); mean daily dose: 20.1 ml/kg/d (range, 8–40.5 ml/kg/d) Median duration of administration 4 days (range, 1–11 d)	Neither administration of HES, the HES dose or number of HES days were associated with an increased risk for AKI
Boyd et al. (102)	Prospective randomized controlled blinded clinical trial in dogs prescribed a fluid bolus of at least 10 mL/kg	Dogs (HES = 21; CRYS = 19)	6% HES 130/0.4 vs. Hartmann's solution	Urine biomarkers of AKI (NGAL, cystatin C, KIM, clusterin, and osteopontin) and VAKI staging system	Concentrations of osmolality-indexed biomarkers prior to and 6, 12, and 24 h after the first study fluid bolus where compared in linear mixed-effects models. The maximum VAKI score up to 7 days during hospitalization and in-hospital mortality	Mean volume of study fluid was not significantly different between groups (HES: 23.1 mL/kg, CRYST: 25.9 mL/kg)	No differences in change over time of urine AKI biomarkers in dogs treated with 10 to 40 mL/kg HES or CRYST over 24 h VAKI scores and mortality were not significantly different between groups

AKI, acute kidney injury; CRYS, isotonic crystalloids; HES, hydroxyethyl starch; NGAL, neutrophil gelatinase-associated lipocalin; KIM1, kidney injury molecule-1; OR, odds ratio; VAKI, Veterinary Acute Kidney Injury.

parameters for clot firmness remained within reference ranges and no statistically significant differences in standard coagulation tests were found between the HES and crystalloid group (112). The clinical relevance of the aforementioned changes has not yet been conclusively determined because actual bleeding tendencies have been evaluated in only one study in dogs. In this study, no clinical bleeding was detected after 10 ml/kg of 6% HES 600/0.75 administered to healthy anesthetized dogs. HES coagulopathy appears to last <3 h [15 ml/kg of 6% tetrastarch (106)] and <24 h [20 ml/kg of 6% hetastarch (113)], respectively, after a single bolus in healthy dogs.

Additional findings in several *in vivo* studies were a significant decrease in hematocrit and platelet count after a HES bolus (106, 112) which was disproportionate to the administered volume of HES (i.e., greater decrease in hematocrit after HES than after crystalloid). The reason for this disproportionate decrease in hematocrit has been proposed to be mobilization of plasma volume previously retained within the endothelial glycocalyx (25).

Recommendations for HES Use in Small Animals

In general, HES should be avoided if the animal responds already to crystalloid or other therapy. HES is not a replacement for albumin and in patients with severe hypoalbuminemia, natural colloids (such as plasma products or albumin) should be considered. In complex cases (such as sepsis or septic shock), therapy is multimodal, and potentially natural colloids and/or vasopressors are necessary. The current evidence favors a very limited risk for HES-associated AKI in dogs and cats when administered in small doses (<20 ml/kg) for short periods of time. Previously healthy animals with acute hypovolemia (e.g., trauma-induced hemorrhage) could inconsequently tolerate administration of HES in the initial resuscitation phase, and HES can be considered if substantial amounts of crystalloids are required. The necessity for colloids is questionable as isotonic or hypertonic crystalloids usually provide adequate resuscitation endpoints in such patients. Administering HES to hemodynamically stable patients and patients with pre-existing azotemia is not recommended.

Based on extrapolated data from people, resuscitating critically ill and specifically septic patients with HES might be detrimental especially in high doses and for long periods of time. Furthermore, as mentioned previously, it might also be futile because damage to their EG exacerbates extravasation of any fluid. Currently, there is no evidence that HES has any disadvantages in veterinary patients with sepsis; however, there are no proven benefits to date either.

The effects of HES on different coagulation tests seem to be mild in dogs without preexisting coagulopathy, and mild to moderate in those with preexisting coagulopathy when using doses <20 ml/kg. Given the evidence in human medicine (definite increased risk of bleeding) and the unclear association between standard laboratory tests and actual clinical bleeding risk in dogs, monitoring of coagulation parameters and clinical bleeding as well as hematocrit and platelet count should be considered if the HES dose is ≥10 ml/kg in patients with potential preexisting coagulopathy, anemia, or thrombocytopenia (112).

In contrast to human medicine and specifically high-income countries, veterinarians need to incorporate financial considerations in their decision-making. Furthermore, prompt expensive therapy might be hindered by owner indecisiveness (whether on financial or personal grounds) or availability. In such instances, HES could be considered as a short-term solution in patients where more costly therapies (i.e., allogenic albumin and plasma products) are unaffordable or while decisions are made. Hydroxyethyl starch should be used as a bolus at the lowest possible dose. Under consideration of the existing literature, the authors recommend a dose for 6% tetrastarch of 5–10 ml/kg for dogs and 3–5 ml/kg in cats over 10–15 min in states of hypovolemia. This can be repeated if needed up to a total dose of 20 ml/kg. The authors do recommend against the use of HES as a CRI, as the effects on COP is negligible (56) and a significant association was found between days of administration of HES and AKI grade (98). Kidney function should be monitored after HES exposure—according to human studies up to 90 days after exposure. Veterinary clinicians should consider discussing the potential adverse effects of HES with owners of septic patients.

GELATIN

Characteristics of Gelatin Solutions

Gelatin solutions contain bovine gelatin hydrolysate, chemically modified to increase solubility. Gelatin preparations have a mean molecular weight of ∼30 kDa. As this is below the renal threshold for glomerular filtration, most of the gelatin is excreted into the urine within minutes of infusion. Thus, the volume effect (70–80%) and the duration of volume expansion (2–3 h) are expected to be more limited compared with HES (114). Gelatin is available as a 4% succinylated gelatin solution in normal saline or in a buffered, polyionic isotonic carrier solution (**Table 1**). Gelatin was withdrawn from the US market in 1978 due to concerns of increased blood viscosity and coagulation impairment (115). In addition, animal experiments suggest harmful effects on kidney structure and function similar to the effects seen with HES (116, 117) (**Figure 1**). In countries where gelatin is still licensed (e.g., Germany, Switzerland), it is contraindicated in severe renal failure. However, there is no clear dose or maximum daily limit, and the recommendation on the package insert states that the "maximum daily dose is determined by the degree of hemodilution." Due to the restrictions in HES use, gelatin could potentially become an alternative synthetic colloid in many European countries.

Adverse Effects of Gelatin in People

Significantly fewer clinical studies on gelatin exist in human medicine as compared with HES. Despite the lack of RCTs evaluating the risks and benefits of intravenous gelatin in people, clinicians in human medicine seem to have increased their use of gelatin following the HES restrictions from 2013 and 2018 (118, 119). There is nonetheless evidence that gelatin might be at least as detrimental to kidney function as HES with a more limited understanding of the underlying mechanism. In a prospective

study in people with severe sepsis, AKI occurred in 70% of patients receiving HES and in 68% of patients receiving gelatin, vs. 47% of patients receiving crystalloids (120). In a systematic review and meta-analysis of gelatin-containing plasma expanders vs. crystalloids and albumin in people, the authors concluded that gelatin solutions increase the risk of anaphylaxis, and may increase bleeding, renal failure, and mortality. The authors recommended against the use of gelatins (119). A prospective currently ongoing study, Gelatin in ICU and Sepsis (GENIUS), is a double-blind RCT investigating the efficacy and safety of gelatin as opposed to crystalloid administration in two parallel groups of patients with severe sepsis/septic shock (NCT02715466). Results from that study are expected end of 2021.

Adverse Effects of Gelatin in Small Animals

Gelatin seems to be rarely used in small animals. According to an international survey about the use of colloids in small animals from 2016, gelatin was used by only 4% of the respondents (in contrast to 85% who used HES), although it was the main synthetic colloid used by 24% of respondents from the UK (5). This finding might be the result of reduced availability of HES products in specific countries (e.g., the UK recalled all HES products from the market in 2013 after the EMA review was initiated). Therefore, veterinarians were forced to use alternative licensed options such as gelatins. Only a few reports of the effects on coagulation and renal injury in dogs, and no reports in cats have been published (95, 111, 121–123).

In regard to its effects on coagulation, experimental studies have shown that 20 ml/kg of 4% gelatin leads to impaired platelet function (111), but that 10 to 20 ml/kg of 4% gelatin had negligible effects on thromboelastography and plasma coagulation (111, 123).

Regarding its renal effects, gelatin led to a marked increase in urine and plasma renal biomarkers, e.g., a 33-fold increase in urinary neutrophil gelatinase-associated lipocalin and a 5.9-fold increase in the urinary concentration of clusterin (a renal glycoprotein induced in response to a variety of injuries including ischemia/reperfusion) (95). Notably, this increase was significantly more than after the same dose of 6% tetrastarch. The same study found prominent renal epithelial cell microvesiculation in all dogs receiving 4% gelatin, although these were not sufficiently severe to meet the definition of "osmotic nephrosis" (95). As mentioned earlier, these data cannot be directly extrapolated to critically ill dogs and cats. However, preexisting renal damage in critically ill and septic patients favors the pathogenesis of osmotic nephrosis-related AKI, and certainly predisposes patients even more to gelatin-induced AKI.

Recommendations for Gelatin Use in Small Animals

According to the results of a small number of studies, the administration of gelatin significantly impairs platelet function and is associated with a high risk of renal injury in dogs. Because the volume-expanding effects of gelatin are inferior to HES, yet the risk of renal injury is significant, it is not appropriate to use gelatin as an alternative to HES.

DEXTRANS

Characteristics of Dextran Solutions

Dextrans are neutral, high-molecular-weight glucose polysaccharides synthesized from sucrose by the bacteria *Leuconostoc mesenteroides* or *dextranicum* (114). Commercially available dextran solutions have an average molecular weight of either 70 kDa (dextran-70) or 40 kDa (dextran-40). Concentrations used are 3, 6, and 10%, and they are mixed in either isotonic or hypertonic electrolyte solutions (**Table 1**) (1, 124). Dextran is either excreted by the kidneys or metabolized by hepatic dextranase and the glucose monomers are ultimately oxidized to carbon dioxide and water (1). Dextran-40, consisting of smaller molecules, has more particles per unit weight than dextran-70, and hence it is more osmotically active. However, its smaller molecular fractions pass faster through semipermeable membranes of the capillaries into the interstitial space and through glomeruli into the urine. Thus, the volume expansion effect of 10% dextran-40 is 150% with a duration of action of 3–5 h, while the volume effect of 6% dextran-70 is 100% with a duration of action of 6–8 h (up to 20 h), due to its larger molecular fractions and prolonged excretion (125). Hypertonic 10% dextran-40 leads to an initial volume expansion of up to 200% (114).

Major adverse effects in people include anaphylactoid reactions, AKI, and impaired coagulation. Several theories about the mechanism for dextran-induced AKI have been proposed, with some of these mechanisms shared with other colloids. These include an increase in plasma COP with subsequent decrease in glomerular filtration pressure and reduced GFR; precipitation of dextran within the renal tubules forming occluding casts and osmotic nephrosis (66, 126, 127) (**Figure 1**). Dextran is also known to impair coagulation, with a subsequent increased risk of bleeding (128). The underlying mechanisms are not well-understood, but bare similarities with other synthetic colloids. These include inhibition of platelet aggregation by reducing the activity of factor VIII, von Willebrand factor, and the glycoprotein IIb/IIIa receptor, affecting fibrinogen polymerization by co-binding, and enhancing fibrinolysis by increasing the circulating levels of tissue type plasminogen activator, and decreasing the levels of plasminogen activator inhibitor-1 (128–130).

According to a 2010 international study (3), the use of dextran in people was widespread in Scandinavia. However, it remained the least used colloid, accounting for only 3% of the total international responders. Dextran has been withdrawn from the human market in several countries (i.e., Germany, Switzerland) but seems to replace HES in others (e.g., Sweden) (131).

Adverse Effects of Dextrans in People

Anaphylactoid reactions after dextran are the result of preformed endogenous anti-polysaccharide antibodies, which cross-react with dextran molecules, causing an immune reaction (114, 132). These severe reactions are prevented by "hapten inhibition" using dextran 1, which binds dextran-reactive antibodies and forms inactive complexes. The dextran 1, which has been used for hapten inhibition since the 1980s, can be administered a few

minutes before the infusion of the main solution of dextran. A 35-fold reduction in anaphylactoid reactions after introduction of the prophylactic use of hapten inhibition was reported in a study from Sweden from a decade after its introduction (133).

Numerous cases of AKI after administration of 10% dextran-40 have been published (69, 134–137). While these older studies have shown an increased risk of AKI with the use of dextran-40, studies of dextran-70 are few, probably because of its limited use worldwide. However, existing data suggest that dextran-70 is also a potential risk factor for the development of AKI in patients with septic shock (138, 139).

Impairment of *in vitro* coagulation and increased bleeding after dextran-70 has also been found in different patient groups (131, 138, 139). Due to this particular side effect, dextran was used as a prophylactic agent against postoperative thrombo-embolism in the 1980 (140).

Adverse Effects of Dextrans in Small Animals

In the 1990s, hypertonic saline with 6% dextran-70 (HSD) preparations were studied in different canine shock scenarios, such as septic, endotoxic, hemorrhagic, and traumatic shock, and gastric dilatation volvulus. As part of developing "small volume resuscitation" strategies, the volume effects of dextran were compared with isotonic crystalloids (141–146). In all mentioned studies, bolus therapy with 4–5 ml/kg of HSD solution was found to be a more effective resuscitation solution compared with an isotonic crystalloid, and 8–10 times less volume was necessary to reach similar cardiovascular endpoints. To the authors' knowledge, there are no reports about dextran-induced anaphylactoid reactions or AKI in dogs. Two studies evaluated hemostasis after dextran-70 in dogs and found a dose-dependent impairment in different hemostatic variables (such as plasma coagulation assays, platelet numbers, factor VIII coagulant activity, von Willebrand factor antigen concentration, and platelet function and buccal mucosal bleeding time) (122, 147). It is likely that as the preference of synthetic colloids shifted toward HES solutions, clinical studies of dextrans in dogs or cats were no longer performed. This may change in the near future. In a recent experimental study in dogs, resuscitation after hemorrhagic shock with HSD showed a similar hemodynamic response compared with Ringer's lactate at 10 times the volume of HSD, but HSD showed superior efficacy in organ protection (kidneys, lungs, and liver) (148).

Recommendations for Dextran Use in Small Animals

Dextran-70 seems to be efficient for volume resuscitation in dogs, especially when combined with hypertonic saline. Other than coagulation impairing effects, adverse effects are largely unknown, and as for other colloids, nephrotoxic effects are likely. There are insufficient data in dogs, and no data in cats, to make a recommendation for dextran use.

ALBUMIN

Characteristics of Albumin Solutions

Solutions of human serum albumin are prepared from pooled human serum, with sterile water as the carrier. The solutions available for intravenous use contain no preservative, and pathogen inactivation is performed by pasteurization at $>60^{\circ}$C for 10 h (149, 150). It is usually available as 5, 20, and 25% solutions, with availability varying geographically. Albumin accounts for ∼50% of the plasma protein content and is responsible for about 80% of the plasma COP (151, 152). A near exponential relationship exists between albumin concentrations and *in vitro* COP, which is explained by the Gibbs–Donnan effect (153). The negative charges on amino acids within albumin attract cations (which have and osmotic effect), leading to a disproportional increase in COP (153). Thus, a 5, 12.5, and 25% HSA solution exerts a COP of ∼20, ∼95, and >200 mmHg, respectively (153).

Albumin is incorporated into the EG, where it contributes to vascular integrity, and normal capillary permeability. In addition, albumin has antithrombotic, antioxidant, and anti-inflammatory properties (55, 154). Hypoalbuminemia occurs as a result of many critical diseases such as systemic inflammation, sepsis, burns, liver failure, protein-losing enteropathy/ nephropathy, and severe prolonged malnutrition. Severe hypoalbuminemia can lead to gastrointestinal complications (i.e., gastric and intestinal edema, gastrointestinal ileus), effects on coagulation (i.e., hypercoagulability, increased platelet aggregation), delayed wound healing, and consequences secondary to the decreased COP (i.e., tissue edema, body cavity effusions) (152). Furthermore, hypoalbuminemia has been associated with high morbidity and mortality rates in human and veterinary patients (100, 155, 156). A meta-analysis in critically ill hypoalbuminemic human patients found that each 10 g/L decrease in serum albumin concentration increased the odds of mortality by 1.37 (156). Nevertheless, it remains unclear whether these effects are a direct result of the albumin deficit, in which case albumin replacement would be beneficial, or if it is merely a marker for the disease severity, and albumin optimization would not lead to improved patient outcomes.

Use of Albumin in People

Albumin is commonly used for fluid resuscitation in people (157–159). Usually, 5% HSA (and more rarely 20% HSA) is administered as a second-line treatment after crystalloids (24, 159, 160). Another indication is correction of significant hypoalbuminemia. Albumin is not only used in conditions requiring COP support. In severe liver diseases such as cirrhosis albumin is recommended for its non-oncotic properties such as antioxidant, scavenging, immune-modulating, and endothelial protective functions (161). Albumin solutions are used in various settings and conditions including priming cardiopulmonary bypass circuits, therapeutic plasma exchange, nephrotic syndrome, and pancreatitis (159). They are not indicated as a nutritional source to raise serum albumin *per se* without hypovolemia (159). Anaphylactoid reactions have been reported in <0.1% of recipients (162).

The use of albumin in critical care has generated controversy for decades. In 1998, a Cochrane systematic review of 30 small RCTs suggested harmful effects (i.e., increased mortality) of albumin as compared with crystalloids for volume replacement in critically ill patients (163). The impact of this meta-analysis was dramatic and led to a substantial reduction in the use of albumin in some countries. In 2004, the "SAFE" study was published, a RCT which compared mortality in 6,997 critically ill patients with hypovolemia who had received 4% albumin *or* saline for intravascular-fluid resuscitation (164). A small volume sparing effect was observed during the first 4 days in the albumin group (ratio of albumin to saline was ∼1:1.4), but no significant difference was found in 28-days mortality, length of hospitalization, or organ dysfunction. Consequently, albumin was considered to be "safe," but that it did not offer any advantage over saline. Subgroup analyses revealed that patients with severe sepsis treated with albumin tended to show a better survival, although the difference did not reach statistical significance ($p = 0.09$) (164). In 2014, the "ALBIOS" trial was conducted in 1,818 patients (158). This RCT aimed to answer the question of whether in patients with severe sepsis or septic shock, administration of 20% HSA to maintain a serum albumin level ≥3 g/dl (≥30 g/L) reduces all-cause mortality at 28 days compared with no albumin. Similarly to the SAFE study (164), there was no significant difference in either the 28- or 90-days mortality or total organ failure scores. Patients who received albumin had a lower daily positive fluid balance over the first 7 days (158).

Despite the theoretical benefits of albumin and efforts to translate this into positive patient outcomes (158, 164), no RCT has yet demonstrated a significant advantage of albumin over other types of fluid, including crystalloids (165). Nevertheless, an increase in albumin use in adult intensive care patients was found recently (6). Albumin appears to have replaced HES as a resuscitation solution (6, 166). This is potentially associated with the Surviving Sepsis Campaign from 2016 which recommend volume replacement with albumin (instead of a synthetic colloid) when patients require "substantial" amounts of crystalloid during hemodynamic stabilization (167).

Adverse Effects of Albumin in Small Animals

In small animals, intravenous albumin is mostly used to correct hypoalbuminemia and COP. Sources of albumin in dogs and cats include CSA, allogenic plasma products, and HSA. No feline-specific albumin products are available (**Table 1**). Canine albumin (e.g., lyophilized canine albumin) manufactured in the USA is currently not ubiquitously available. Consequently, some veterinarians are forced to use HSA products if they wish to administer concentrated albumin to dogs and cats. Human albumin shares ∼80% structural homology with canine albumin (168); therefore, allergic reactions are possible. Anaphylactic and other immune reactions, and life-threatening complications have been reported in dogs after administration of 5, 10, and 25% HSA (169–173). Relevant study results are summarized in **Table 3** and are explained in more detail later.

In 2007, two research groups observed profound adverse reactions after 25% HSA was administered to healthy, non-hypoalbuminemic dogs (169, 170). Cohn et al. (169) administered 25% HSA twice, 5 weeks apart, to nine healthy dogs. Anaphylactic shock (collapse, hypotension, hypothermia, tachypnea, vomiting, and diarrhea) occurred within minutes in one out of nine dogs after the first dose of HSA, and in two out of two dogs receiving a second dose, while the second HSA infusion for the remaining seven dogs was abandoned. Furthermore, two out of nine dogs developed urticaria and edema 1 week after administration, and all developed anti-HSA antibodies. Similarly, Francis et al. (170) administered 25% HSA to six healthy dogs. One out of the six developed anaphylactic shock, and all dogs developed a delayed type III hypersensitivity including lameness, edema, vasculitis, and vomiting. Two of the dogs died at 21 and 28 days after HSA administration, despite intensive care treatment. These two dogs developed disseminated intravascular coagulation, AKI, and pulmonary edema. All six dogs were found to have anti-HSA antibodies (170).

Eight publications have reported the effects (including adverse effects) of administration of HSA in critically ill hypoalbuminemic dogs and cats in a clinical setting (171–175, 177–179). Human serum albumin resulted in increased serum albumin concentrations and COP (173, 174, 176, 178) and increased systemic blood pressure (174). Two studies reported higher serum albumin concentrations in survivors after HSA administration (173, 176) and in one study the magnitude of serum albumin increase was positively associated with survival (173). All but one of the aforementioned studies (171–175, 177, 179) reported adverse reactions in some patients, of which a few were severe or fatal. One prospective study in 40 cats reported no adverse effects after administration of 5% HSA (178). Most studies were retrospective in nature and adverse effects of HSA may have remained undetected or unrecorded. Furthermore, the definition and recognition of adverse reactions is not uniform between studies.

The available literature suggests that administration of HSA induces severe adverse reactions predominantly in healthy, normoalbuminemic dogs and may induce only mild or no adverse reactions in critically ill patients. Several possible explanations for this discordant response have been proposed. Supraphysiologic concentrations of albumin might be partly responsible for acute adverse reactions in healthy normoalbuminemic dogs. Therefore, administration of HSA over a longer period (e.g., 12–24 h) or administration of diluted albumin solutions may result in fewer immunologically mediated adverse effects (170, 175, 178). Further, it is possible that deterioration of the clinical condition or death in critically ill patients have been incorrectly attributed to the underlying disease, rather than to an adverse reaction (170). It is also possible that some hypoalbuminemic dogs given HSA may not have survived long enough to develop a type III hypersensitivity reaction (170). Lastly, it is speculated that critically ill dogs may be immunosuppressed (due to the severe underlying disease) and therefore not respond as strongly to HSA as healthy

TABLE 3 | List of small animal publications using human serum albumin solutions and its doses.

Author (year [references]	Species	Setting	Albumin concentration	Total dose	Dose per hour*	Duration of administration	Adverse events
Mathews and Barry, (174)	64 dogs 2 cats	Retrospective study, critically ill	25%	Mean: 1.25 g/kg	0.025–0.43 g/kg/h	Range 4–72 h	Facial edema in 2 dogs
Trow et al. (173)	73 dogs	Retrospective case series, critically ill	10%	Median 1.4 g/kg (range 0.1–6)	∼0.12 g/kg/h	12 h	23% acute adverse reactions (mild: tachypnea, tachycardia, increased temperature, peripheral edema, and ventricular arrhythmias; severe: coagulopathies, cardiac arrest). 4% delayed complications
Vigano et al. (175)	418 dogs 170 cats	Retrospective study, critically ill	5%	Mean: 1 g/kg/day	0.1 g/kg/h	Dogs: Median 96 h (range 28–264 h) Cats: Median 72 h (range 48–168 h)	No acute severe adverse reaction. Minor acute adverse reactions (diarrhea, hyperthermia, and/or tremors) in 43.5% dogs and 36.5% cats (no specific treatment)
Powell et al. (172)	2 dogs	Case series, critically ill	5%	Dog 1: 1.4 g/kg Dog 2: 1.3 g/kg	0.35 g/kg/h 0.43 g/kg/h	4 h 3 h	Type III hypersensitivity reaction (leukocytoclastic vasculitis and dermal antigen-antibody complexes) 8-16 days after exposure
Horowitz et al. (176)	22 dogs + 17 negative control dogs	Retrospective study, septic peritonitis	25%	Mean: 2.55 g/kg (range: 0.95–6.38)	n/a	Mean: 39.2 h (range: 11–98 h)	No evaluation for adverse reactions
Loyd et al. (177)	21 dogs	Retrospective study, PLE	25%	Dose: 0.5 g/kg	∼0.16–0.25 g/kg/h	2–3 h	2/21 acute reaction; 1 dog euthanized 2/21 delayed reaction; 1 euthanized
Vigano et al. (178)	40 cats + 20 control cats	Prospective study, critically ill	5%	Mean: 0.72 g/kg (range: 0.5–1)	0.07–0.1 g/kg/h	Mean: 7 h (range: 5–10 h)	No acute or delayed adverse reaction
Mazzaferro et al. (171)	2 dogs	Case series, septic peritonitis	25%	Dog 1: 1.5 g/kg Dog 2: ∼2.6 g/kg	0.13 g/kg/h 0.33 g/kg/h	12 h 8 h	Delayed type III hypersensitivity reaction with AKI; euthanasia
Martin et al. (179)	14 critically ill + 2 healthy dogs 21 critically ill + 47 healthy dogs	Prospective, healthy and critically ill	25%	Healthy: 1st time 0.5 g/kg 2nd time 0.25 g/kg Critically ill: Median: 1.3 g/kg (0.45–11.8)	0.25 g/kg/h 0.125 g/kg/h 0.2 g/kg/h	2 h 1 h	Critically ill: transient fever in 1 dog, no other acute or delayed adverse reaction Healthy: 1st time: facial edema in 1 dog day 8 2nd time: acute adverse reaction in both dogs
Cohn et al. (169)	9 dogs	Prospective study, healthy	25%	1st time: 2.5 g/kg (9 dogs) after 5 weeks 2nd time: 2.5 g/kg (2 dogs)	0.66 g/kg/h	Mean: 3.75 h (range 3–4.5 h)	1/9, acute hypersensitivity (1st time) 2/2 acute hypersensitivity (2nd time) 2/9 urticaria/ edema after 2 weeks (1st time) 9/9 developed anti-HSA antibodies
Francis et al. (170)	6 dogs	Prospective study, healthy	25%	0.5 g/kg	0.5 g/kg/h	1 h	6/6 Delayed type III hypersensitivity reaction

**Doses were converted into grams according to data in the publications; PLE, protein loosing enteropathy; h, hours.*

immunocompetent dogs (169, 170). This was challenged by a recent case series of two critically ill hypoalbuminemic dogs with septic peritonitis receiving 25% HSA (171). These dogs developed a delayed type III hypersensitivity reaction with AKI, hypoalbuminemia, proteinuria as well as immune complex deposition and vasculitis. As the use of HSA increases, more reports of allergic reactions might be expected to emerge thus proving a fuller picture on HSA safety in animals.

Both healthy (169, 170, 179) and critically ill dogs (179) developed anti-human albumin antibodies within 7 days after administration of 25% HSA. Antibody concentrations were highest 4–6 weeks after HSA administration in the critically ill dogs. Interestingly, one study reported that 7% of dogs had anti-HSA antibodies without previous HSA infusion (179). The latter could be attributed to cross-reaction with anti-bovine albumin antibodies that developed when dogs were exposed to bovine albumin through vaccination or ingestion (180). This not only shows that HSA albumin should not be administered over longer periods of time (several days), but also some patients might be previously sensitized to the molecule and show reactions on initial administration.

Canine serum albumin was evaluated in two prospective, small-scale, clinical studies. One study evaluated 14 dogs with septic peritonitis and found increased serum albumin concentrations, COP, and Doppler blood pressure 2 h after CSA administration. No acute or delayed adverse events were found (181). In a second study (presented in an abstract form to date), six healthy Beagles received CSA at a dose of 1 g/kg at three different time points (on days 1, 2, and 14). Dogs were monitored for evidence of transfusion-associated complications during the infusions and at 1, 2, 12, and 24 h after each infusion. The follow-up period was 28 days. The authors concluded that repeated infusions appeared safe, with no adverse changes to physical examination, hematologic, or biochemical parameters (182).

Recommendations for Albumin Use in Small Animals

In contrast to people, albumin solutions in small animals have been mainly used to increase and maintain plasma albumin concentrations (CRI over hours and days) in patients that may or may not be cardiovascularly unstable. Only one study to date has shown an association of albumin administration and increased patient survival (173). Immediate and delayed adverse reactions in some critically ill dogs have been observed in several studies, with some of them proving fatal (169–172, 174, 177, 179). Critical illness does not seem to be protective against adverse immune reactions to HSA solutions. Cats seem to be less sensitive to HSA transfusions compared with dogs; however, this is based on only three studies with a total of 211 cats (174, 175, 178). Due to the potential adverse effects, HSA should be considered only for severely hypoalbuminemic patients in which the use of isotonic crystalloids alone carries a high risk of edema and/or in which hypoalbuminemia itself is a greater risk factor than the potential adverse effects of HSA. Autologous albumin products should be used when possible. Intravenous HSA or CSA is not a substitute for a proper nutritional management in critically ill patients.

Depending on the hydration status of the patient, albumin administration may be considered at plasma albumin concentrations below 10–15 g/L (1.0–1.5 g/dl) (173–176, 178). Albumin supplementation should discontinue once the serum concentration has reached 20–25 g/L (2.0–2.5 g/dl) (152). The recommended formula for calculation of the albumin dose is dose albumin (g) = (desired albumin g/L – patient albumin g/L) × 0.3 × kg body weight (171) over 12–24 h. In the authors' experience, this formula overestimates albumin requirements, so we recommend re-evaluating plasma albumin concentration after 50% of the calculated dose and adjusting requirements accordingly. Alternatively, a dose of 2 g/kg over 10 h is recommended (183). Some authors prefer to administer diluted HSA (5 or 10%) which may be better tolerated due to a more physiological COP (173, 175, 178), but there is no conclusive proof for fewer adverse effects compared with the more concentrated form. The described length of administration varies between authors from 4–6 h (184) to 12 h (173) to several days (174, 175). Based on current literature, it is not clear whether the length of administration, the total dose, or both have an influence on delayed adverse reactions. Supraphysiological concentrations are not desired as it might lead to suppression of hepatic albumin synthesis (152).

ALLOGENIC PLASMA PRODUCTS

Use of Allogenic Plasma Products in People

The two major indications for administration of fresh frozen plasma (FFP) in people are to prevent hemorrhage and to stop active bleeding (185). Common clinical scenarios involving the use of FFP include liver failure, reversal of anticoagulant toxicity, temporary treatment of coagulation factor deficiencies, cardiopulmonary bypass surgery, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura (185). Its use has also been reported in patients with acute pancreatitis, uremic syndrome, and severe burns (185). Furthermore, FFP is a component of "massive transfusion" protocols and used in patients with traumatic coagulopathy. Substantial controversy surrounds the indications and efficacy of administration of FFP in people (186–195). While the evidence of its efficacy in preventing or stopping bleeding is somewhat robust, other less common indications are not evidence based.

Use of Allogenic Plasma Products in Small Animals

In veterinary medicine, FFP is most commonly used to prevent or stop bleeding (196). However, its indications extend beyond treating or preventing coagulopathies. Fresh frozen plasma is administered as a means of albumin supplementation as well as a volume expander (197, 198). It is specifically advocated to prevent further dilution of albumin and clotting factors that can result from the administration of large volumes of crystalloids or synthetic colloids. Clear guidelines for the use of FFP in veterinary patients are lacking (196). To the authors' knowledge,

there are no studies investigating the effects of FFP specifically when used for fluid resuscitation.

Several retrospective studies have documented the reasons for FFP administration in small animals. In a 1999 study, 74 dogs received FFP to provide albumin in 63%, coagulation factors in 47%, α-macroglobulin in 10%, and immunoglobulins in 13% of patients (197). Another retrospective study compared the use of FFP in 283 dogs and 25 cats between two decades (1996–1998 and 2006–2008) (198). The main reasons for FFP use were coagulopathies, hypoalbuminemia, and acute pancreatitis (i.e., provision of α-macroglobulin). In the later decade, significantly more FFP was used for the treatment of coagulopathies, while significantly less FFP was used to counteract hypoalbuminemia or support patients with acute pancreatitis. Fresh frozen plasma has been advocated for administration to people with pancreatitis, and, by extrapolation, to dogs (199). The rationale for the use is to supplement plasma α-macroglobulin. This is a broad-acting protease inhibitor that prevents intravascular damage caused by circulating activated pancreatic proteases. Alpha-macroglobulin becomes depleted during the systemic inflammation (200). A multicenter RCT in people from 1991 demonstrated no benefit of administering high-volume FFP to patients with acute severe pancreatitis (201). Hence, the practice to use FFP in people with pancreatitis has long been overturned. One retrospective study compared the outcome of dogs with pancreatitis that had been or had not been given FFP (202). In that study, dogs that had received FFP had a higher mortality, and no benefit was apparent. As the authors did not control for the severity of illness, and FFP is more likely to be administered to more severely affected patients, this might have biased the results (202). Two recent retrospective studies evaluated FFP transfusions in cats. One study in 36 cats found that coagulopathies were the most common reasons for FFP transfusion (94% of cats) (203). The other study evaluated FFP transfusions in 121 cats and found coagulopathies (83%), hemorrhage (35%), and hypotension (25%) to be the main reasons for administration (204). Median doses reported in dogs are 14 ml/kg (small dogs) and 5 ml/kg (large dogs), due to the administration per unit or ½ unit per dog (197). Another study reported median doses of 15–18 ml/kg (198). One study reported median doses of 6 ml/kg in cats (204).

Two retrospective studies evaluated effects of FFP transfusion in dogs. Median prothrombin time and activated partial thromboplastin time were significantly decreased after plasma transfusion. Notably, pre- and post-transfusion serum albumin and COP were not different in patients receiving FFP. In addition, no association was found between the volume of infused FFP and outcome (198). Another study focusing on adverse effects of blood product administration in dogs reported 8% mild adverse reactions after FFP transfusions (205) compared with 22% after pRBC administrations. This contrasts with the findings in people where transfusion reactions after administration of FFP are more common than after pRBC transfusions and include life-threatening acute lung injury, and circulatory overload (185). The aforementioned retrospective studies also evaluated effects of FFP administration in cats. In one study on 36 cats, coagulation parameters seemed to improve in 90% of the cats after transfusion (203). Fifteen percent of the cats experienced potential transfusion reactions, including respiratory signs, fever, and gastro-intestinal signs. In the other study (121 cats), Doppler blood pressure increased, and they were significantly less likely to be coagulopathic after transfusion. Similarly, 16% of the cats had possible reactions, such as increased body temperature (64% of cats with reactions) and tachypnea/dyspnea (47% of cats with reactions) (204).

Recently, cryopoor plasma (CPP), a byproduct of the production of cryoprecipitate, has been used as an albumin source (206–208). The albumin concentration in canine CPP is significantly higher than in FFP, suggesting that it may be a possible treatment for hypoalbuminemia in dogs while avoiding volume overload (207). A retrospective study of 10 critically ill dogs found that plasma albumin increased after a CPP CRI (206). The dogs received a median total dose of 31 ml/kg CPP over a median duration of 16 h and a mean rate of administration of 1.8 ml/kg/h. In a recent case report (a 44-kg dog with septic shock secondary to enterectomy dehiscence), CPP was used as a source of canine albumin and intravascular volume. In this case, CPP was provided for a total volume of 58 units CPP over 9 days (approximately CPP 227 ml/kg). The authors proposed that CPP CRI may be a viable alternative to CSA (and HSA) for oncotic support and albumin replacement, but multiple units from different donors may increase the risk of an adverse reaction. Cryopoor plasma is only available in specialized institutions or commercial veterinary blood banks.

Recommendations for Plasma Products Use in Small Animals

With the decline in use of synthetic colloids and in countries where albumin solutions are either not available or not popular, plasma products might be the only natural colloid alternative. However, the current evidence is not sufficient to enable strong recommendations for the use of plasma products in small animals. Allogenic plasma transfusions seem to have a low risk for adverse effects, although cats seem to be more sensitive than dogs. As an albumin source, the administration of plasma (either FFP or CPP) appears to be relatively safe, although large volumes might be necessary. Fresh frozen plasma contains ∼30 g/L (3.0 g/dl) of albumin. If the goal of the plasma transfusion is to achieve adequate albumin supplementation, substantial volume per kilogram is needed, particularly when dealing with ongoing albumin loss [i.e., 22 ml/kg of plasma to raise the albumin concentration by 5 g/L (0.5 g/dl)] (152). Administering such volumes, potentially derived from various donors, should be weighed against the risk of volume overload and other transfusion reactions. The use of CPP rather than FFP, where volume expansion is not required, might prevent volume overload. Because these products are usually administered per unit (or ½ unit), because of the necessity to thaw, dose regimens (in ml/kg) vary depending on patient size. Fresh frozen plasma should not be used as a first-line volume expander unless specifically indicated. This is because it is a valuable and expensive resource that should not be wasted, and it is a potential source of

adverse reactions in already debilitated animals. Furthermore, it technically cannot be administered as a first-line volume expander due to the necessity to thaw, which takes 30–45 min (209). However, if other indications for FFP administration (e.g., overt or imminent coagulopathy) are present, FFP can be considered as part of resuscitative efforts. While established dosing regimens for FFP as a volume expander do not exist, the authors recommend similar doses as other natural or synthetic colloids.

HEMOGLOBIN-BASED OXYGEN CARRIER (HBOC) SOLUTIONS

Hemoglobin-based oxygen carrier (HBOC) solutions consist of chemically purified and polymerized bovine hemoglobin (Hb) suspended in a crystalloid carrier fluid. The hemoglobin in those solutions is a colloid with a high molecular weight (up to 250 kDa in some) and a relatively high COP. Several products have been developed over the last few decades, seeking the advantage of a long shelf-life and low infectious risk alternative to pRBC transfusions (210). The safety and efficacy of HBOCs has been evaluated in various species mostly through experimental studies and have yielded conflicting results. In hemorrhagic shock models, HBOCs seem to show promising efficacy in restoring cardiovascular parameters and in some studies parallel the oxygen carrying capacity of pRBCs (211–219). However, they are associated with considerable adverse effects such as systemic vasoconstriction, pulmonary and systemic hypertension, reactive oxygen species formation, and renal and myocardial injury (220, 221). As a consequence, HBOCs are not currently authorized for use in people (222).

The use of HBOCs has been described two small-scale clinical studies in dogs. In a prospective randomized study in 20 dogs with GDV, five times smaller volumes of Oxyglobin (OPK Biotech Netherlands BV) were required to achieve resuscitation end-points as compared with HES 450/0.7 (223). Another prospective randomized study compared the use of Oxyglobin and pRBC in 12 anemic dogs with babesiosis. The authors concluded that Oxyglobin had comparable effects with pRBC, with the exception that dogs treated with pRBC had a quicker return to habitus and appetite (224). In a retrospective study about the clinical use of Oxyglobin in 48 cats, a high risk of life-threatening circulatory overload was found in cats suffering from cardiac disease (225). Oxyglobin was authorized by the European Medicines Agency and Food and Drug Administration for use in anemic dogs in 1999 (212–214). However, it has been withdrawn from the market in most countries. Recently, a new highly purified low molecular weight (65 kDa) bovine blood–derived HBOC (Oxapex; New A Innovation Ltd., Kowloon, Hong Kong) has been authorized for use in anemic dogs in New Zealand and awaiting authorization in Australia, the USA, Canada, and the EU (**Table 1**). A canine hemorrhagic shock model showed improved hemodynamics, lactate, base excess, and tissue oxygenation after administration of various doses of Oxapex (226). In this study, high doses led to significant increases in pulmonary artery pressures (226). Further studies are required to establish the safety and efficacy of this new product.

CONCLUSION

Colloids, both natural and synthetic, were originally used with narrow indications. For instance, the original purpose of synthetic colloids was a cheap, long shelf-life "bridging fluid" to remain in the intravascular space while soldiers wounded on the frontline were transported to the field hospital where further stabilization took place. The original purpose of natural colloids was to replace missing blood components (albumin, clotting factors, fibrinogen) in various patients. In the decades that followed, their indications have expanded far beyond their original purpose, such as perioperative fluid therapy for HES and volume expansion for albumin. The expansion of their indications to potentially higher doses and use over longer periods of time (specifically for HES) may have contributed to more and more severe adverse effects being observed and, in some instances, has led to severe restrictions in their use.

Admittedly, veterinary emergency and critical care medicine does, to some extent, take into account the guidelines adopted in human medicine. However, veterinary medicine cannot directly follow the "attitudes" adopted in human medicine because of species differences, different patient cohorts, the availability and safety of some products, and the need to incorporate the owner's financial considerations into the decision-making process. Therefore, species-specific guidelines should be established.

We are living in an era where fluids are recognized as drugs with indications, contraindications, and adverse effects. Therefore, to ensure rational utilization of colloids in the face of weak and contradicting evidence, the authors recommend prescribing colloids on a case-by-case basis, similarly to prescribing any other drug.

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K-NA and IDY performed the literature search and wrote the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Intravenous Fluid Administration and the Coagulation System

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Intravenous fluid administration in veterinary patients can alter coagulation function by several mechanisms. Both crystalloid and colloid fluids cause hemodilution, reducing platelet count and plasma coagulation protein concentrations. Hemodilution is associated with a hypercoagulable effect at low dilutions and a hypocoagulable effect at higher dilutions. Composition of crystalloid fluids likely has a minor effect, primarily dependent on fluid ion composition. Hypertonic crystalloids may also cause hypocoagulability. Colloids, both synthetic and natural, can cause hypocoagulability by several mechanisms beyond the effects of hemodilution. These include impaired platelet function, decreased plasma coagulation factor activity, impaired fibrin formation and crosslinking, and accelerated fibrinolysis. The vast majority of the veterinary literature investigates the hypocoagulable effects of hydroxyethyl starch–containing fluids using *in vitro*, experimental, and clinical studies. However, results are inconsistent, likely due to the varying doses and physicochemical properties of the specific fluid products across studies. In addition, some evidence exists for hypocoagulable effects of gelatin and albumin solutions. There is also evidence that these colloids increase the risk of clinical bleeding in people. Limitations of the veterinary evidence for the hypocoagulable effects of colloid fluids include a predominance of *in vitro* studies and *in vivo* studies using healthy subjects, which exclude the interaction of the effects of illness. Therefore, clinical relevance of these effects, especially for low-molecular-weight hydroxyethyl starch, is unknown. Firm recommendations about the most appropriate fluid to use in clinical scenarios cannot be made, although it is prudent to limit the dose of synthetic colloid in at-risk patients. Clinicians should closely monitor relevant coagulation assays and for evidence of hemorrhage in at-risk patients receiving any type of fluid therapy, especially in large volumes.

Keywords: 0.9% saline, colloid, crystalloid, dilution coagulopathy, gelatin, hydroxyethyl starch

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INTRODUCTION

Intravenous (IV) administration of crystalloid and colloid fluids can affect coagulation function by hemodilution, as well as through factors related to the composition of the fluid (**Box 1**). The mechanisms are multifactorial, affecting platelet function, coagulation factor concentration, and clot strength, and vary between fluid types. The majority of the literature pertaining to

BOX 1 | Summary of mechanisms by which different fluid types alter coagulation function.

Crystalloids and colloids

- Hemodilution
  - Hypercoagulability at low dilutions, possibly due to reduced antithrombin activity
  - Hypocoagulability at higher dilutions, due to reductions in platelet number and plasma coagulation factor concentration

Colloids (synthetic and natural)

- Impaired platelet function
  - Reduced expression/accessibility of fibrinogen receptor integrin $\alpha_{IIb}\beta_3$
  - Non-specific binding to the platelet surface
  - Acquired type 1 von Willebrand disease
- Decreased plasma coagulation factor activity
  - Specific decrease in factor VIII
  - Non-specific decrease in all factors
- Impaired fibrin formation and crosslinking
  - Qualitative differences in fibrin clot
  - Inhibition of factor XIII interaction with fibrin
  - Inhibition of thrombin interaction with fibrinogen
- Accelerated fibrinolysis
  - Enhanced conversion of plasminogen to plasmin
  - Reduced inhibition of plasmin by α_2-antiplasmin

veterinary medicine includes *in vitro* studies, using blood from healthy animals, and *in vivo* studies, administering fluids of concern intravenously to healthy animals. Some studies have also examined effects of fluids on coagulation in experimental animal models of disease, as well as in clinical patients. These study designs each have advantages and limitations. *In vitro* or healthy animal studies are better able to elucidate subtle mechanistic interactions with coagulation, without the confounding effects of illness. However, their clinical relevance may be difficult to interpret. The downside of utilizing disease models or clinical patients is that subtle differences in coagulation are often not detected without large sample sizes because of variability caused by the illness itself or other aspects of clinical management. The authors have endeavored to provide a broad survey of the available data regarding the effects of fluids on coagulation in companion animals. The reader is encouraged to evaluate the breadth of the evidence presented herein and to choose the most relevant data for their specific patients.

Abbreviations: ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; AT, antithrombin; BMBT, buccal mucosal bleeding time; CFT, clot formation time (in the ROTEM assay); CT, clotting time (in the ROTEM assay); FVIII, coagulation factor VIII; HES, hydroxyethyl starch; LRS, lactated Ringer solution; MA, maximum amplitude (in the TEG assay); MCF, maximum clot firmness (in the ROTEM assay); MW, molecular weight; PCT, platelet closure time (as measured by the PFA-100); PFA-100, platelet function analyzer; PT, prothrombin time; ROTEM, rotational thromboelastometer; TEG, thromboelastograph; vWF, von Willebrand factor.

HEMODILUTION

The dilutional effects of fluid administration on the coagulation system are proportionate to the degree of hemodilution. The effects include decreasing platelet number, but not function, and decreasing procoagulant and anticoagulant [e.g., antithrombin (AT)] proteins to varying degrees (1). The effect of hemodilution is often not the sole purpose of studies assessing coagulation; however, it is often accounted for by the addition of a control group that receives isotonic crystalloid fluid only, or blood diluted with crystalloid only. Therefore, the effects of hemodilution can be surmised by assessing before-and-after changes in control groups within these studies. This evidence on the effects of hemodilution is discussed in detail in the following section on crystalloid fluids.

When comparing the effects on coagulation between fluid types, there are some important considerations concerning hemodilution and the relevant pharmacodynamics of the fluids. It can be challenging to validate the degree of hemodilution between groups in *in vivo* studies. There are a range of methods to measure degree of hemodilution, including utilizing the dilution of endogenous (e.g., hemoglobin, albumin) or exogenous (e.g., indocyanine green) markers, none of which are perfect (2, 3). Thus, the exact degree of hemodilution, or blood volume expansion, caused by different fluid types can vary between studies. However, there is strong evidence that the magnitude and duration of blood volume expansion following administration of synthetic colloid are greater than those of an equal volume of isotonic crystalloid. This may be context-sensitive and dependent on the integrity of the endothelial surface layer, although this relationship is not fully understood (4–7). Studies in healthy dogs (8) and people (9) demonstrated 3- to 4-fold greater hemodilution for dextran, hydroxyethyl starch (HES), and gelatin colloids than isotonic crystalloid. However, the subjects were euvolemic prior to fluid administration, and the fluid doses exceeded common clinical practice. Colloids also had a greater volume effect than crystalloids in healthy dog and pig models of non-traumatic hemorrhagic shock, after fluid redistribution (10–12). Conversely, in an experimental model of orthopedic surgery, dogs administered 10 mL/kg of either high-molecular-weight (MW) HES or balanced isotonic crystalloid showed a similar drop in packed cell volume 1 h postinfusion (13). Clinical trials in critically ill hypovolemic people (14–18) and dogs (19) show that blinded clinicians targeting self-defined clinical endpoints administer on average 1 to 1.5 times the volume of isotonic crystalloid compared to HES, much less than the 3- to 4-fold difference predicted by experimental studies. The targeted endpoints could include normalization of mean arterial blood pressure, heart rate, blood lactate concentration, or central venous pressure, among other clinician-specific criteria. While this may indicate lack of a beneficial colloid osmotic effect in critical illness, it is important to note that the degree of blood volume expansion was not measured in these trials. The volume

of fluid administered may simply reflect usual clinical practice. While these uncertainties make it difficult to exactly apportion hypocoagulability following fluid administration into dilutional and non-dilutional components, it is the overall effect that is clinically relevant.

CRYSTALLOIDS

The evaluation of *in vitro* crystalloid effects on coagulation has been primarily focused on isotonic crystalloids, although some studies have also evaluated hypertonic solutions. The effect of crystalloids on coagulation is thought to be primarily dilutional; however, variability in the ionic and buffer composition of the fluids may be relevant, specifically with regard to calcium ion content and fluid pH. Most *in vitro* studies have been designed to evaluate the putative effect of a bolus of different amounts of crystalloid, in ratios varying from 4 to 20% of crystalloid to blood, to mimic clinically relevant infusion volumes. Overall, the effects on coagulation appear proportionate to the degree of dilution, with measurable effects generally occurring beyond 20% dilution, or one part fluid to four parts blood.

Saline 0.9%

Saline 0.9% has been extensively studied because of its use as a diluent for many HES and dextran formulations. In most studies, the dilutional effect on platelet count is not addressed, although it may decrease with increasing dilutions. This may result in some of the recorded changes, especially in platelet dependent assays (e.g., aggregometry). In humans, a 40% *in vitro* dilution of whole blood with 0.9% saline results in decreased platelet function as measured by the Impact cone and plate analyzer (20). Using the platelet function analyzer 100 (PFA-100), *in vitro* 10, 20, 30, and 40% dilutions of human whole blood with 0.9% saline demonstrated a dilution-dependent prolongation of the platelet closure time (PCT) (21, 22). Despite these changes, whole-blood (impedance) platelet aggregometry using adenosine diphosphate (ADP) or collagen as agonists was unaffected by a 5%, 10%, 15%, or 20% *in vitro* dilution with 0.9% saline (22, 23). Platelet aggregometry (impedance or optical) is a low-shear test for platelet function, whereas the PFA-100 uses high-shear conditions. Platelet responses to agonists vary between shear conditions, and platelets under high-shear conditions are reliant on von Willebrand factor (vWF) for adhesion (24). Differences in shear velocities are relevant because they may be representative of platelet performance under venous (low-shear) or arterial (high-shear) conditions. Similar results were seen using optical aggregometry, where aggregation to ADP and collagen was unchanged from baseline at 10% and 20% dilution, but was impaired at 40% (25). It is unclear if platelet count was standardized across dilutions in this study; therefore, absolute platelet count may have affected results. The impairment in this case was not different from that seen with 40% dilution with 6% low MW HES, making it difficult to distinguish between dilutional and functional impairment. In a different assessment of platelet function, the *in vitro* addition of 0.9% saline to human whole blood in dilutions ranging from 2.5 to 30% did not affect platelet P-selectin expression or fibrinogen binding following ADP stimulation (26).

Several *in vitro* studies in dogs have not detected an effect of 0.9% saline on PCT using ADP/collagen cartridges at 10% dilution but have identified mild prolongation at 20% dilution (27–30). One of these studies documented platelet count for each dilution, reflecting that some samples at 20% dilution had a platelet count below the manufacturer's recommended minimum for assessment of platelet function (29). Therefore, the mild prolongation in PCT is likely due to dilution of platelets.

Viscoelastic coagulation evaluation of *in vitro* 0.9% saline dilution of whole blood demonstrated changes consistent with hypercoagulability in some human studies, although it is unclear if this is an artifact or should be a clinical concern. Using thromboelastography (TEG), Roche et al. described slightly increased clot strength and increased rate of clot formation when whole blood was diluted with 0.9% saline at 20% to 40% dilutions (31). At a 60% dilution, the TEG indicated hypocoagulability (31). Other studies have identified decreases in clot strength with a 40% *in vitro* dilution (20, 25). Overall, minimal change in coagulation status occurs at *in vitro* 0.9% saline dilutions $<$20% (23). Using another viscoelastic measurement (Sonoclot), no changes in clot rate or strength were seen following addition of 0.9% saline to whole blood at 20% or 40% dilutions (32, 33). The slight increase in coagulability with modest hemodilution with 0.9% saline may be due to diluted AT, allowing faster thrombin formation, or may be an artifact. The overall clinical relevance is uncertain. In rotational thromboelastometry (ROTEM) studies of *in vitro* 0.9% saline dilution of whole blood, impaired platelet function appears to play less of a role than fibrinogen in the decreased clot firmness (34–36). This is inferred from greater effects seen on the FibTEM test, where platelet function is excluded, than comparable effects on baseline tests.

In dogs, *in vitro* addition of 0.9% saline to whole blood at a 20% dilution appeared to cause relative hypocoagulability using the ExTEM test, which is a tissue factor–initiated ROTEM test (statistical significance not noted) (27). This was characterized by prolonged time to initiate clotting, decreased speed of clot formation, and lower clot strength. However, another study using 10 and 20% dilutions of canine whole blood failed to document significant changes using ROTEM (37).

In vivo, a 10 mL/kg IV infusion of 0.9% saline given to healthy people failed to prolong PCT (collagen/epinephrine and collagen/ADP cartridges), change TEG parameters, or alter flow cytometric assessment of platelet fibrinogen binding or P-selectin expression following activation by ADP or thrombin receptor–activating peptide (21, 38). Another study that administered 1 L of 0.9% saline IV to healthy volunteers demonstrated hypercoagulability on TEG, including shortened R time with increased angle and maximum amplitude (MA) (39). This equates to ∼15 mL/kg, resulting in a 9% decrease in hematocrit. This same study documented decreases in fibrinogen and AT concentrations, and the authors hypothesized that the decreased AT may have caused the observed hypercoagulability. A further study by this group, whereby healthy people received 14 mL/kg of a 0.9% saline bolus, showed that the induced hypercoagulable effect was transient, dissipating as the bolus was redistributed

(40). Using optical aggregometry, Ruttmann et al. also noted a slightly increased aggregation response to high-dose (100 μmol/L) ADP and to ristocetin (1.2 mg/mL) in humans following a 1 L IV bolus of 0.9% saline (39).

In healthy dogs, a 20 mL/kg IV bolus of 0.9% saline given over an hour resulted in no change in the PCT, which remained within the reference range (41). A hemorrhagic shock study in greyhound dogs compared 80 mL/kg of 0.9% saline to 20 mL/kg of low MW HES administered IV after removal of 48 mL/kg of blood (42). It showed mild prolongation of PCT in both groups, consistent with dilution; however, a slightly greater magnitude of change was observed in dogs that received 0.9% saline. In healthy ponies, an IV infusion of 80 mL/kg of 0.9% saline given over 2 h did not result in changes in cutaneous bleeding time, vWF antigen activity, prothrombin time (PT), or activated partial thromboplastin time (aPTT) (43). Another study of a 10 mL/kg IV bolus of 0.9% saline given to adult horses showed a transient prolongation of PT and aPTT 1 h after the completion of the bolus (44). Additionally, a transient decrease in factor VIII (FVIII) activity was seen in these horses, although there was no change in vWF activity as a result of the bolus (44). Following this bolus, mild transient hypocoagulability was demonstrated using viscoelastic assessment, but platelet function as measured by PFA and optical aggregometry was unaffected (44).

Polyionic and Ringer Solutions

With regard to hemostasis, the composition of crystalloid (polyionic vs. saline) may result in differential effects, although the magnitude of these effects may not be clinically relevant. One meta-analysis of the human literature suggested that the use of 0.9% saline was associated with greater blood loss compared to lactated Ringer solution (LRS) when used in high-risk patients (45). Proposed mechanisms included the presence of calcium ions in LRS or the effect on coagulation of a saline-induced hyperchloremic acidosis.

Similar to 0.9% saline, the *in vitro* addition of LRS to human whole blood in dilutions ranging from 2.5 to 30% did not affect the expression of P-selectin or fibrinogen binding following ADP stimulation (26). Serial dilutions of human whole blood with LRS did result in significant increases in the rate of clot formation (TEG angle), most prominent at the 30 to 50% dilutions and progressing to hypocoagulability above a 50% dilution (31, 46). In another report, a 33% dilution of human whole blood with LRS did not change the Sonoclot signature from baseline; however, at a 66% dilution, the signature indicated hypocoagulability (32). These changes were corroborated using ROTEM and TEG analysis as well, with significant thrombocytopenia and hypocoagulability following *in vitro* dilution of human whole blood with LRS (47). The hypocoagulable effect of LRS on viscoelastic testing could be ameliorated by correcting the platelet count in the diluted sample (48). Another report evaluating the viscoelastic coagulation monitoring (ROTEM and Sonoclot) effects of *in vitro* dilutions of human whole blood with LRS did not show significant differences (49).

In cats, a 14% dilution of whole blood with Ringer acetate resulted in ROTEM hypocoagulability, as seen by prolongations in clotting time (CT; InTEM assay) and clot formation time (CFT; ExTEM and InTEM assays), and reduced maximum clot firmness (MCF; ExTEM, InTEM, and FibTEM assays) and alpha (ExTEM and InTEM assays) (50). Dose-dependent hypocoagulabilty was demonstrated on TEG analysis with addition of LRS to canine whole blood (16%, 33%, and 66% dilution), showing progressively decreasing angle and MA starting from either 16% dilution or 33% dilution, respectively (51).

In vivo studies conducted in healthy individuals have shown mixed results in regard to the effects of administered polyionic solutions; however, most lean toward mild hypocoagulability. A 10 mL/kg IV bolus of LRS given to healthy people failed to prolong PCT using either ADP/collagen or epinephrine/collagen cartridges, compared to baseline (52). In dogs administered a 15 mL/kg IV bolus of modified acetate-containing Ringer solution, no change in PCT or ROTEM values was seen, compared to baseline (53). In the context of experimental severe hemorrhage, dogs resuscitated with LRS (total of 50 mL/kg IV) and stored whole blood (in equal volume to shed blood) showed little alteration in measured PT and aPTT, but appeared to have decreases in activity of factors II, V, VII, VIII, and X, compared to baseline (statistics not shown) (54). In healthy dogs anesthetized for orthopedic surgery that received an IV bolus of 10 mL/kg LRS, PT, aPTT, FVIII:C, and vWF:Ag did not change significantly when measured 1 h after the bolus (13). A mild prolongation of buccal mucosal bleeding time (BMBT) was seen in these dogs, accompanied by a transient decrease in platelet count, but without effects on platelet aggregation in response to platelet activating factor. In rabbits, hemodilution achieved by replacement of 40% of estimated blood volume with five times that volume of LRS resulted in hypocoagulability in both TEG and traditional coagulation testing (55). In this study, it appeared that procoagulant coagulation factors were decreased in excess of anticoagulant factors (e.g., AT, protein C) (55).

Despite the paucity of clinical veterinary studies to draw upon in this area, one observational study in dogs with parvoviral enteritis compared TEG changes in dogs that received bolus fluid therapy (median, 26.5 mL/kg) to those that received a smaller amount (median, 10 mL/kg) (56). Dogs that received bolus therapy showed relative hypercoagulability, but also likely had more severe disease. Resuscitation corresponded with a lower median HCT and higher platelet concentration from admission values for both groups, with a decreased AT activity in the group that received a larger volume of LRS. In both groups, the fibrinogen concentration was above the assay detection limit (700 mg/dL), raising the question of the role of fibrinogen in maintaining *ex vivo* coagulation competency in animals with severe inflammation that are aggressively resuscitated (56).

Hypertonic Crystalloid

The effects of hypertonic saline on coagulation have been assessed in a limited number of reports. *In vitro* addition of 7.2% saline to canine whole blood prolonged PCT (ADP/collagen cartridge) at both 4% and 10% dilutions, compared to undiluted blood (27). In this study, hypocoagulability was seen in ROTEM analysis, specifically in prolongation of the ExTEM CFT and decrease in MCF. Similar findings were seen when 3% saline was added to canine whole blood at an 11% dilution, with prolonged PCT,

increased ExTEM CT and CFT, and reduced ExTEM MCF (57). In dogs with intracranial hypertension given 4 mL/kg of 7.2% saline over 5 min, no significant change in PCT was detected, despite the median PCT being outside of the reference interval immediately after the bolus and 1 h later (58). The only change in ROTEM analysis of these patients was a slightly shortened CT in the FibTEM assay, which is likely not clinically relevant, and was not seen in the prior *in vitro* study (57). In another study where healthy dogs were given 5 mL/kg of 7.5% saline IV at a rate of 1 mL/kg per minute, no change was detected in TEG parameters up to 3 h after the end of the infusion (59).

Overall, the effects of administration of large volumes of crystalloid can cause hypocoagulability, primarily through dilutional effects, and without clear distinction between fluid types. Caution should be used in animals receiving large amounts (>40 mL/kg) of crystalloid, especially in those at increased risk of bleeding. A balanced resuscitation protocol with fresh frozen plasma to maintain concentrations and activity of the key coagulation factors should be considered in patients at increased risk of bleeding (1) with the overall context of the patient kept in mind. Despite these recommendations, the effect of crystalloid on coagulation tests may be transient, considering its redistribution to the extravascular space, and may not necessarily result in clinically relevant hemorrhage, depending on individual patient comorbidities.

COLLOIDS

Synthetic colloid-containing fluids are commonly administered for fluid resuscitation in small animals (60) and horses (61). They are favored by some veterinarians for their potential to maintain intravascular colloid osmotic pressure and expand blood volume more effectively for a given infused volume than isotonic crystalloids (8, 43, 62). However, they have the potential to cause hypocoagulability through dilutional and non-dilutional mechanisms, including direct effects on platelets and coagulation factors. Along with other adverse effects, the documented clinical relevance of colloid-induced hypocoagulability has led to decreased use of synthetic colloids for fluid resuscitation in human critical care (63). While similar hypocoagulability has been demonstrated in veterinary species, the clinical relevance is unclear at this time. This section will broadly review the mechanistic data for the coagulation effects of synthetic colloids and then detail evidence concerning HES and gelatin separately. Lastly, a brief review of the effects of exogenous albumin administration will be provided.

Mechanisms of Hypocoagulability

Synthetic colloids cause a dilutional coagulopathy proportionate to the degree of blood volume expansion, which may be of greater magnitude than that from the same infused volume of isotonic crystalloid. There are several additional mechanisms by which synthetic colloids may lead to impairment of coagulation. These include intrinsic platelet dysfunction, acquired von Willebrand disease, a specific decrease in FVIII activity, non-specific decreases in all coagulation factor activity, impaired fibrin formation and crosslinking, and accelerated fibrinolysis.

Reduced cell surface expression, or reduced accessibility for ligand binding, of the activated fibrinogen receptor integrin $\alpha_{IIb}\beta_3$ (previously known as glycoprotein IIb–IIIa) has been demonstrated by flow cytometry of human platelets. This includes samples collected from patients undergoing elective surgery treated with HES of varying MW (21, 38) or platelets treated with HES or gelatin *in vitro* (21, 38, 64). Effects of gelatin on this fibrinogen-binding receptor may depend on the type of gelatin tested; reduced, increased, and no effect on expression have all been reported (see below for further discussion on the effect of calcium in diluent) (64). Binding of HES to the platelet surface has also been demonstrated by flow cytometry of human platelets treated with abciximab, a monoclonal antibody that blocks HES binding to integrin $\alpha_{IIb}\beta_3$ (65). This is often viewed as non-specific coating of platelets by HES, although the molecular basis is not fully understood. Platelet adhesion may also be impaired because of reduction of the activity of vWF (43, 44, 66–71). A study of human patients administered HES demonstrated an equal decrease in all vWF multimers, characterizing this as acquired type 1 von Willebrand disease (72). Gelatin interferes with collagen binding of vWF, not the absolute concentration; therefore, it may form a complex with the coagulation factor, prompting its excretion (66).

Functional platelet studies have demonstrated a reduction in platelet adhesion and activation, as evidenced by prolonged PCT (21, 38), although not all studies consistently show this effect. Although gelatin interferes with ristocetin-induced aggregation (66, 67, 73–75), it mostly fails to impair aggregation stimulated by other agonists (66, 76–80). The effect of gelatin on PCT is also mixed between species (64, 81).

Given the close association between vWF and FVIII, which circulate as a bound complex, it is unsurprising that synthetic colloids also cause a reduction in the activity of FVIII (67–69, 72, 74, 82, 83). It has been postulated that binding of colloid molecules to the vWF–FVIII complex may accelerate its urinary excretion, although to the authors' knowledge there are no data to support this (72, 84). While the secondary coagulation effects of synthetic colloids are usually described as affecting FVIII specifically, one study of HES administration in dogs showed reductions in other coagulation factors (82). There were concurrent reductions in the concentration of other plasma proteins, along with increases in these proteins in the lymph, leading to the hypothesis that the colloid osmotic effect of synthetic colloids leads to extravascular relocation of proteins. Additionally, an *in vitro* study suggested that AT activity is maintained following hemodilution with HES, in contrast to the decrease in activity seen with crystalloid hemodilution (85).

The strength of the fibrin clot is impaired by synthetic colloids. Fibrin clots formed in the presence of HES or gelatin are qualitatively different from those formed in undiluted blood, with increased turbidity and mass/length ratio (86), and reduction in clot density or weight (87–89). Images obtained by scanning electron microscopy show less fibrin meshwork when blood is diluted with either gelatin (**Figure 1**) or HES, compared to dilution with 0.9% saline (88). Administration of HES to rabbits caused impaired clot propagation and final clot strength by inhibiting the interaction of factor XIII and fibrin, with

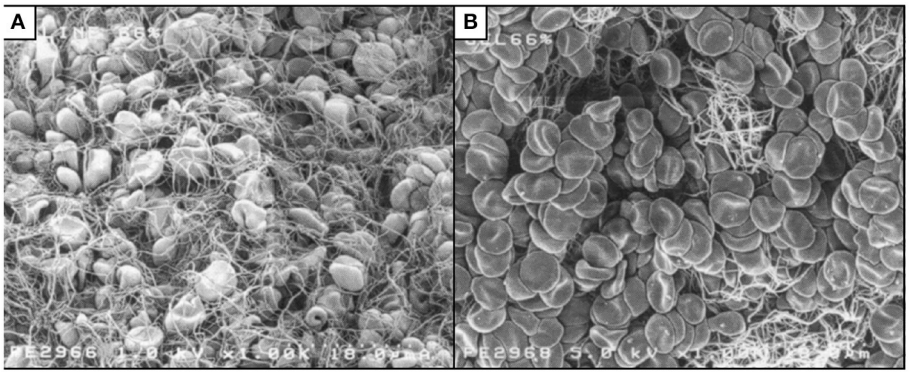

FIGURE 1 | Scanning electron micrographs of whole blood diluted to 66% with 0.9% saline **(A)** or succinylated gelatin **(B)**. Less fibrin meshwork is visible with gelatin dilution. Reproduced with permission (88).

a secondary mechanism of inhibition of thrombin–fibrinogen interaction (90). Studies in people (*in vitro* and *in vivo*) have also demonstrated a reduction in FXIII, although this is in line with a reduction in other coagulation factors (73, 91). Adding FXIII and fibrinogen back into solution in an *in vitro* study partially corrected coagulation impairment created by gelatin but not that associated with HES (91). Also, infusing fibrinogen concentrate after gelatin in a porcine hemorrhagic shock model improved clot characteristics and reduced blood loss, compared to placebo (89).

Clots formed in the presence of HES are also susceptible to accelerated fibrinolysis. Decreases in the urokinase-activated clot lysis time, a measure of fibrinolysis, have been demonstrated *in vitro* in human plasma mixed with HES and in blood collected from healthy human volunteers administered HES (92). Enhanced conversion of plasminogen to plasmin by urokinase has been demonstrated in the presence of dextran (93). Additionally, dilution of plasma with HES led to reduced inhibition of plasmin by α_2-antiplasmin (94).

Many of these mechanistic studies are several decades old and were often conducted with a limited range of coagulation assays. For example, whereas some studies have postulated a specific effect against FVIII, most did not measure the activity of other coagulation factors and so cannot exclude broader effects. Additionally, some of the studies have contradictory findings. These may relate to experimental technique, statistical methods, sample size, or differences between the specific colloids investigated. Often the types of colloid studied are no longer in clinical use. Older colloids such as dextran and high MW HES are believed to have greater effects on coagulation than modern low MW HES and gelatin. Thus, the exact mechanisms of colloid-induced hypocoagulability and how much they vary between different types of colloids are still unclear. More recent research, including the bulk of the veterinary literature, has focused on the effects of specific synthetic colloid fluids on clinically applicable coagulation assays and clinical outcomes.

Hydroxyethyl Starch

The synthetic colloid most commonly administered in veterinary medicine is HES, a synthetic polymer of amylopectin with hydroxyethyl modification at the C2, C3, and C6 positions (60). There are many HES products that differ in concentration, average MW, molar substitution (average number of hydroxyethyl modifications per glucose subunit), C2/C6 ratio (location of hydroxyethylation), the raw material from which they are manufactured (maize or potato), and the carrier solution (balanced crystalloid or 0.9% saline) (84, 95, 96). Higher MW and molar substitution delay degradation and are associated with greater impairment of coagulation. Varieties of HES with MW of >400 kDa are considered high MW, whereas 200–400 kDa is considered medium MW, and <200 kDa is considered low MW. Despite the extensive literature on the effects of HES in many species, this section will focus on the use in dogs, cats, and horses.

In vitro studies have mostly demonstrated dose-dependent impairment of coagulation following dilution of blood with different types of HES, compared to crystalloid controls. Common to these studies are measurements of platelet function and viscoelastic tests of coagulation. *In vitro* dilution of canine blood with high MW HES consistently causes hypocoagulability beyond dilution, as measured by TEG (97, 98) and ROTEM (27). Two of those studies also assessed platelet function and did not show any effect beyond dilution on PCT (27, 98). However, in another canine study, dilution with high MW HES showed significant prolongation of PCT, compared to 0.9% saline dilution (30). The only canine *in vitro* study of medium MW HES showed significant prolongation of PCT, compared to 0.9% saline (29). Additional canine *in vitro* studies have used low MW HES, with mixed results. Platelet dysfunction has been demonstrated by changes in PCT (28) or a flow chamber model (99). Other studies measuring PCT have failed to detect an effect beyond dilution with low MW HES (27, 29, 98). Hypocoagulability beyond dilutional effects has also been demonstrated for low MW HES using TEG or ROTEM in three canine studies (27, 37, 98), but was not detected in a fourth (51). The only *in vitro* study of HES dilution of equine blood showed that both high and low MW HES caused significant platelet dysfunction and hypocoagulability, as measured by PCT, TEG, Sonoclot, optical platelet aggregometry, and activities of vWF and FVIII, with

many changes in excess of the crystalloid controls (70). The only feline *in vitro* study showed that blood diluted with HES had ROTEM evidence of hypocoagulability beyond that of the balanced isotonic crystalloid control (50). Most *in vitro* studies did not report fibrinolysis data from viscoelastic testing.

A range of *in vivo* experiments have investigated changes in platelet function and viscoelastic testing after HES administration to healthy animals. High MW HES increased PCT in healthy dogs when administered as a 20 mL/kg bolus (41), compared to a crystalloid control, or a constant rate infusion of 1 to 2 mL/kg per hour, compared to baseline (100). Bolus administration of 15 mL/kg of low MW HES to healthy dogs caused PCT prolongation and ROTEM evidence of hypocoagulability beyond dilution (53). However, a slow infusion over 2 h of 10 mL/kg of low MW HES to healthy dogs did not cause any changes in coagulation times or TEG parameters (101). Administration of 10 to 20 mL/kg boluses of high MW HES to healthy horses decreased vWF and FVIII activity (43, 44) and caused PCT prolongation beyond the effects of dilution (44). In the latter study, low MW HES caused similar alterations in coagulation, but of a lower magnitude, and persisting for a shorter time (12 vs. 24 h). Another study of healthy horses that were administered low MW HES showed some evidence of hypocoagulability on TEG with 20 and 40 mL/kg bolus doses (102). However, a different study found no effects on TEG and only minor changes in PT and fibrinogen concentration with a 10 mL/kg bolus (103). The only study of the coagulation effects of low MW HES in healthy foals found that fibrinogen concentration was decreased with a 20 mL/kg bolus, compared to a balanced isotonic crystalloid control (104). Other plasma coagulation assays did not show significant differences to the balanced isotonic crystalloid control, but platelet function and viscoelastic tests were not assessed. As with the *in vitro* experiments, most of these studies did not assess fibrinolysis.

Additional *in vivo* experiments have been performed in models of surgery, hemorrhage, and systemic inflammation. In a canine model of orthopedic surgery, dogs administered a bolus of 10 mL/kg high MW HES were compared to dogs administered the same volume of balanced isotonic crystalloid (13). There were no differences in plasma coagulation assays, platelet aggregation, BMBT, or surgical hemorrhage. Two canine models of hemorrhage showed evidence of hypocoagulability and platelet dysfunction after the administration of 10 to 40 mL/kg boluses of high MW HES, compared to crystalloid, assessed using whole blood and plasma clotting assays and bleeding times (105, 106). Another early canine hemorrhage study showed hypocoagulable TEG parameters after a total of 50 mL/kg high MW HES, but there was no crystalloid control (107). In a subsequent canine hemorrhage model, high or medium MW HES was administered in combination with hypertonic crystalloid at a total dose of 6 mL/kg (108). Only a small prolongation of PT was detected, compared to an autologous whole-blood control. More recently, no difference in PCT was found when 20 mL/kg low MW HES was compared to 80 mL/kg crystalloid for resuscitation in two similar greyhound models of hemorrhagic shock (42, 81). The more recent of these also included ROTEM analysis, with HES administration prolonging the ExTEM CT significantly more than the crystalloid control (81). In that study, the HES group also had evidence of hypocoagulability when compared to a group resuscitated with 20 mL/kg of fresh whole blood. As the crystalloid group had fewer differences compared to fresh whole blood, the study may have been underpowered to detect all of the differences between HES and crystalloid resuscitation. There was no evidence of hyperfibrinolysis. A different canine model of less severe hemorrhage did not find any differences in platelet count, BMBT, PT, aPTT, or ROTEM between groups given low MW HES and crystalloid to cause hemodilution to a hematocrit of 33% (109). A canine model of systemic inflammation showed that administration of 40 mL/kg IV of low MW HES was associated with TEG evidence of hypocoagulability and a decrease in vWF concentration, changes that were greater than the same volume of 0.9% saline (71). That study also had a healthy control group with similar changes after HES administration. Conversely, in a similar equine model, there was no evidence of hypocoagulability when 10 mL/kg of high MW HES was administered in combination with 5 mL/kg of hypertonic crystalloid, compared to 15 or 60 mL/kg of 0.9% saline (110).

There are very few veterinary clinical studies evaluating the effects of HES on coagulation. In a prospective case series, 26 hypoalbuminemic dogs administered variable dosages of high MW HES were monitored for clinical evidence of spontaneous hemorrhage (111). Serial platelet count, PT, and aPTT were measured in 18 of the dogs. Three dogs developed spontaneous hemorrhage, and five had worsening of one or more coagulation parameters. Given the lack of a control group, it is not possible to determine whether these changes were due to HES by a dilutional or non-dilutional mechanism or to the underlying diseases. Historical case series describing the use of high MW HES in combination with buffered isotonic crystalloid to treat hypotension in 21 cats (112) and 16 dogs (113), both to the authors' knowledge only published in abstract form, did not document any excessive bleeding (both dogs and cats) or increases in activated clotting times (cats only). However, there is little detail on how the treatment was administered or how the animals were monitored. A prospective case series of 24 horses with colitis or surgical colic treated with a 10 mL/kg bolus of medium MW HES showed significant prolongation in aPTT postinfusion, compared to baseline, in the subgroup of horses with large intestinal ileus (114). Given the lack of a control group, it is unclear whether this was consistent with hemodilution alone. There was no methodological detail on how horses were monitored for clinical hemorrhage, but there was a statement that no side effects were noted. A more recent prospective case series in 20 hypoalbuminemic dogs administered low MW HES as a constant rate infusion at 1 or 2 mL/kg per hour for 24 h did not detect hypocoagulability with plasma coagulation assays or ROTEM (115). A recent open-label clinical trial randomized 42 dogs with spontaneous hemoperitoneum to initial stabilization with a bolus of either 10 mL/kg low MW HES or 30 mL/kg balanced isotonic crystalloid (116). Immediately after infusion, there was some ROTEM evidence of impaired clot initiation, propagation, and strength in the HES group, compared to the crystalloid group, with no evidence of hyperfibrinolysis. Hemodynamic parameters were not different between groups

immediately after infusion, but no subsequent monitoring for hemorrhage was reported. A recent abstract evaluated banked samples from a randomized blinded clinical trial comparing bolus administration of low MW HES or balanced isotonic crystalloid in 39 critically ill dogs (117). No differences between fluid groups were detected in a broad panel of plasma coagulation assays over the 24 h after fluid administration.

While many veterinary studies demonstrate laboratory evidence of hypocoagulability in animals administered HES, data on patient-centered endpoints are lacking. Many human clinical trials have compared blood loss and transfusion requirement between patients administered HES and crystalloid. Meta-analyses of these generally suggest that HES is associated with increased blood loss and transfusion requirement. The latest Cochrane review documented an increased transfusion requirement in critically ill patients treated with HES, compared to crystalloid (118). Another meta-analysis suggested that perioperative crystalloid therapy in patients undergoing major non-cardiovascular surgery resulted in less blood loss, compared to patients who received HES (119). Trauma guidelines recommend avoiding HES because of the adverse effects on hemostasis (120).

Gelatin

Gelatin-based colloid fluids have been in clinical use since the 1950s (121) and continue to maintain a presence among current fluid choices. There are three different types of gelatin that have been used over the years: oxypolygelatin, modified fluid gelatin (succinylated gelatin), and urea-linked gelatin (polygeline). They all stem from the hydrolysis of collagen but have undergone different chemical processes in order to create a stable fluid product containing molecules of an appropriate size (122). As they have been reported to have various effects on coagulation, it is important to note which type of gelatin is being referred to when assessing any one study. Gelofusine® (4% succinylated gelatin) and Haemacell® (urea-linked gelatin) have dominated the literature in the last 20 years. Brand names are provided in this section when relevant to either currently available products or the diluent of the product.

Most of the evidence concerning gelatin's effect on coagulation stems from *in vitro* and *in vivo* research in people, with few veterinary studies to draw upon. The dominant features of coagulation perturbation include mild platelet dysfunction, likely due to interference with vWF binding to collagen, and interference with fibrin polymerization, causing more friable blood clots. Similar to HES, *in vitro* studies demonstrate a dose-dependent relationship on the effects of gelatin on platelet function and viscoelastic testing, with changes evident beyond ∼30% dilution and more consistent at 50% or greater.

Gelatin products inhibit platelet aggregation *in vitro* when ristocetin is used to initiate aggregation. This agonist binds to vWF, which then stimulates the GP1b receptor on platelets. Therefore, it is a test of either decreased vWF or dysfunctional vWF. Impaired response to ristocetin seems to be an effect particular to gelatin. *In vitro* studies using human blood have shown that succinylated gelatin decreases platelet aggregation at >40% dilution, compared to crystalloid dilution (78), although some studies have shown no effect beyond dilutional (77). An *in vitro* study in healthy people found a prolongation in PCT with all three types of gelatin that was similar to dilution with 0.9% saline (64). Inhibition of ristocetin-induced platelet aggregation has also been demonstrated *ex vivo*, when succinylated gelatin was administered to healthy people (66), as well as those undergoing either cardiac or orthopedic surgery (67, 73–75). A canine hemorrhagic shock study found significantly longer PCT after dogs were given 20 mL/kg of succinylated gelatin, compared to the same dose of fresh whole blood or low MW HES, or 80 mL/kg of balanced crystalloid (81).

Compared to similar dilutions with crystalloid, *in vitro* dilutions (10%, 20%, and 40%) of human whole blood with succinylated gelatin cause a greater increase in CFT and greater decrease in alpha angle and MCF on ROTEM, particularly at a 40% dilution (77). Similar concentration-dependent changes have been demonstrated with TEG (123, 124). Some differences in clot rate, time to peak, and MA have also been demonstrated with Sonoclot, with succinylated gelatin having a greater effect compared to crystalloid (32, 33, 125). Studies comparing low or medium MW HES and succinylated gelatin have shown that HES causes a greater magnitude of change in some viscoelastic test parameters, compared to gelatin, although the differences are subtle or inconsistent (49, 124, 126–130).

Some studies have compared different types of gelatin to each other, with the most consistent detrimental effects to coagulation being shown for succinylated gelatin. Haemacell® showed minimal to no effects on Sonoclot testing *in vitro,* whereas succinylated gelatin prolonged clot rate beyond the effects of haemodilution (33). Haemacell® has also been shown to have some hypercoagulable effects on TEG, similar to the addition of 0.9% saline to blood at a low dilution (20%) (131). This mild hypercoagulable effect on TEG parameters was also demonstrated in an earlier euvolemic hemodilution study in dogs (107). Conversely, Haemacell® decreases platelet aggregation in response to a range of agonists, whereas Gelofusine® only causes decreased ristocetin-stimulated aggregation (78). These differences between the fluids can be explained by the presence of calcium within Haemacell®, as the effects of Gelofusine® were similar when calcium was added *in vitro* (78). Oxypolygelatin (Gelifundol®) also appears to cause less effect on viscoelastic measurements compared to succinylated gelatin (Gelafusal®) (123), although oxypolygelatin does inhibit ristocetin-induced platelet aggregation, similar to other gelatins (75). Finally, following *in vitro* activation of platelets obtained from human whole blood diluted with various gelatins, Haemacell® increased the expression of integrin $\alpha_{IIb}\beta_3$ receptors, whereas oxypolygelatin (Gelifusin®) had no effect, and succinylated gelatin (Gelifundol®) reduced expression (64).

There are few veterinary reports that document the effects of gelatin on coagulation. Two canine studies assessed platelet function; however, only one controlled for hemodilution (81, 132). This study found a longer PCT after an IV bolus of 20 mL/kg of succinylated gelatin, compared to the same dose of either fresh whole blood or low MW HES, or 80 mL/kg of balanced crystalloid (81). Using a hemorrhagic shock model in dogs, one study showed a slightly increased PT and aPTT

after 20 mL/kg of low MW HES given over 20 min, compared to a similar dose of succinylated gelatin (81). Another study in healthy dogs showed no difference in PT or aPTT after 20 mL/kg of succinylated gelatin given IV over 2 h (101). An older study that compared a range of synthetic colloids in a canine euvolemic hemodilution model found effects on PT and aPTT to be comparable between HES and Haemacell® (107). No change in PT and aPTT was found after 5 mL/kg of oxypolygelatin in a second study, compared to baseline (132). Three of the canine studies assessed viscoelastic coagulation (81, 101, 107), with two studies showing more detrimental effects to the speed and strength of clot formation following HES administration, compared to similar doses of either Haemacell® or succinylated gelatin (81, 107).

Clinical outcomes assessed in human patients administered a gelatin product include surgical blood loss, chest drain output, and packed red blood cell transfusions. Chest drain output is a standard measure of blood loss in cardiac surgery. Other outcomes include organ failure scores, hospitalization times, and mortality. Unfortunately, most of these studies have small sample size, impairing their ability to identify definitive differences between fluid types. The two recent large studies with adequate sample size are not randomized trials, which may have introduced bias into the results. Bearing this in mind, one study in cardiac surgical patients found that perioperative administration of succinylated gelatin was associated with a higher chest drain output, higher grades of bleeding, and more patients receiving red blood cell transfusions, compared to the use of crystalloid (133). The second observational report compared separate 2-year periods during which cardiac surgical patients received a majority of succinylated gelatin, low MW HES, or crystalloid in the perioperative period. In this study, more patients received platelet transfusions in the gelatin group than the other groups, and there was a higher risk of in-hospital mortality in the gelatin group (134). Two limitations included the potential bias of time and contamination of the gelatin group with HES prime fluid during cardiopulmonary bypass. Other smaller studies were not able to identify differences in clinical outcomes between fluid types, either gelatin compared to HES or crystalloid (73, 74, 76, 135–140). There are two exceptions concerning studies in cardiac surgical patients. One small randomized clinical trial ($n = 15$ per group) found that patients receiving HES 200/0.5 received more blood products than those receiving succinylated gelatin (137). This finding was similar in another small randomized clinical trial ($n = 55$ per group) comparing HES 200/0.5 to Haemacell® (141). Given the limitations of sample size and observational design, large randomized controlled trials are needed to determine if gelatin fluid products confer increased risk of clinical bleeding. The number of subjects needed to answer this question may not be feasible in veterinary medicine.

Albumin

The natural colloid albumin also has the potential to cause hypocoagulability. The mechanisms may be similar to synthetic colloids, with impairment of fibrin polymerization a leading hypothesis. Rheologic analysis of samples following *in vitro* dilution of blood from healthy volunteers with 4.5% albumin, low MW HES, or gelatin showed measurements consistent with weaker fibrin clots that were more permeable with less branched polymerization for all three fluids (87). Furthermore, hypocoagulability on ROTEM from *in vitro* albumin dilution can be mostly reversed with the addition of fibrinogen concentrate and factor XIII (142). Impairment of platelet function may also occur, as *in vitro* addition of concentrated albumin to human blood resulted in prolongation of PCT (143). That study also showed ROTEM evidence of hypocoagulability with increasing albumin concentration, despite a method that avoids dilutional effects.

The hypocoagulability caused by albumin appears to be greater than that caused by crystalloids, but less than that caused by synthetic colloids. *In vitro* dilution of human blood with 4% albumin led to greater ROTEM evidence of hypocoagulability than 0.9% saline at a 40% dilution, but not 10 or 20% (144). Another human *in vitro* study showed TEG evidence of hypocoagulability, beyond dilutional effects, with both 30 and 60% dilutions of 5% albumin, but the changes were less than with medium MW HES dilution (124). A similar *in vitro* comparison showed less ROTEM hypocoagulability with albumin dilution than with two low MW HES or succinylated gelatin fluids (128).

Human clinical studies have investigated the effects of 4 or 5% albumin administration on coagulation assays, blood loss, and transfusion requirement. A substudy of the Saline vs. Albumin Fluid Evaluation clinical trial showed that 4% albumin administration was independently associated with aPTT prolongation, but the effect size was small (145). In a clinical trial of cardiac surgery patients randomized to receive LRS, low MW HES, or 5% albumin, there was no difference between groups in the primary outcome of postoperative chest drain output (17). However, both colloid groups received more blood transfusions than the crystalloid group, with no difference between HES and albumin. Both colloids groups showed greater hypocoagulability

BOX 2 | Diagnostic modalities that can detect alterations in coagulation function caused by fluid administration.

Tests of platelet number and function

- Platelet count
- Bleeding times, such as buccal mucosal bleeding time
- Platelet function analyzer-100 (PFA-100) closure time
- Aggregometry
- Flow cytometry
- von Willebrand factor assays

Tests of plasma coagulation factor function

- Coagulation times (prothrombin time and activated partial thromboplastin time)
- Fibrinogen concentration
- Individual coagulation factor assays

Viscoelastic coagulation tests

- Thromboelastography
- Rotational thromboelastometry
- Sonoclot

on ROTEM than crystalloid but with different patterns over time: the HES group was the most hypocoagulable group at ICU admission, whereas the albumin group was most hypocoagulable group at 24 h postoperative. Similarly, in a clinical trial of patients undergoing major surgery, patients randomized to 5% albumin had significantly greater hypocoagulability of TEG parameters than those randomized to LRS, with no difference in blood loss or transfusion (146). There is currently no published veterinary evidence for the effects of either human or canine albumin administration on coagulation. However, as the use of this product potentially increases over time, the effects on coagulation will need to be considered. Additionally, specific indications for albumin in veterinary patients (e.g., hypoalbuminemia due to enteral or renal protein loss) have additional disease-related implications for altered coagulation and should be studied directly.

In summary of the effects of colloids, synthetic colloids and albumin cause a dose-dependent hypocoagulability equal to or greater than that of an equivalent dose of isotonic crystalloids. The evidence for differences between colloid types is not fully elucidated but likely differs based on species and underlying disease. Similar to crystalloids, caution should be used with large doses of colloids and where there are other risk factors for bleeding. Plasma transfusion may partially ameliorate colloid-induced hypocoagulability. However, some adverse effects such as platelet dysfunction may persist.

CONCLUSION

The bulk of the available evidence indicates that IV fluids, when administered in clinically relevant doses, can cause dose-dependent hypocoagulability. Synthetic colloids have a greater potential for causing coagulopathy because of multiple non-dilutional mechanisms. The exact differences between fluid products and the clinical relevance of these effects remain an area of investigation. The published body of literature covers a broad range of species and diseases; targeted recommendations for specific populations are not currently possible. Clinicians should be mindful of the potential for hypocoagulability when administering fluids. We recommend closely monitoring relevant coagulation assays (**Box 2**) and for evidence of hemorrhage in patients receiving fluid therapy and pursuing goal-directed patient-centered resuscitation. Vigilance is especially required in patients with other risk factors for hemorrhage, those receiving a large volume of fluid, or with the use of synthetic colloids. Clinicians should strive for balance across the use of different fluid types and consider replacement of coagulation factors, via plasma transfusion, for bleeding patients where appropriate.

AUTHOR CONTRIBUTIONS

All authors drafted, revised, and approved final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Current Concepts in Fluid Therapy in Horses

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Despite the frequent inclusion of fluid therapy in the treatment of many conditions in horses, there are limited studies available to provide evidenced-based, species-specific recommendations. Thus, equine fluid therapy is based on the application of physiology and extrapolation from evidence in other veterinary species and human medicine. The physiologic principles that underly the use of fluids in medicine are, at first glance, straightforward and simple to understand. However, in the past 20 years, multiple studies in human medicine have shown that creating recommendations based on theory in combination with experimental and/or small clinical studies does not consistently result in best practice. As a result, there are ongoing controversies in human medicine over fluid types, volumes, and routes of administration. For example, the use of 0.9% NaCl as the replacement fluid of choice is being questioned, and the theoretical benefits of colloids have not translated to clinical cases and negative effects are greater than predicted. In this review, the current body of equine research in fluid therapy will be reviewed, connections to the controversies in human medicine and other veterinary species will be explored and, where appropriate, recommendations for fluid therapy in the adult horse will be made based on the available evidence. This review is focused on the decisions surrounding developing a fluid plan involving crystalloids, synthetic colloids, and plasma.

Keywords: fluid therapy, fluid administration, crystalloids, colloids, horse

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INTRODUCTION

Fluid therapy is a key component in treatment and supportive care of horses with a variety of conditions, especially those with critical illness. Despite its frequent utilization, it remains challenging to make evidence-based treatment recommendations. This is due to the limited number and design of studies related to fluid therapy that have been performed in horses (1). The majority of those that have been published are either experimental (healthy or healthy with induced pathology) or retrospective and, therefore, provide only low-level evidence. While there are a handful of prospective, randomized studies in horses, they are marred by small sample size and often have significant case heterogenicity limiting their strength as well. As a result of the minimal species-specific information available, recommendations for fluid therapy often rely heavily on the lowest levels of evidence - expert opinion, theory, physiology, and extrapolation from other animal species and human medicine.

At the simplest level, fluids are drugs and, as such, have the potential for both life-saving benefits and serious, possibly life-threatening, adverse effects. In order to better align their utilization with their characterization as drugs, human medicine has begun a paradigm shift toward considering their use within the "four Ds" of drug therapy: drug, dosing, duration, de-escalation (2). Treating fluids as any other prescription drug ensures appropriate consideration of options and approaches

to maximize their benefits and limit complications. Several current controversies within human medicine can easily be framed within the concept of the "four Ds" and "prescribing" of fluids, involving the choice of route, fluid type, and dose.

Given that equine practitioners must rely heavily on extrapolation, it is not surprising that both recommendations and controversies regarding fluid therapy in horses parallel those in human medicine and other veterinary species. For the purposes of the current review, we will focus on three areas of debate related to the first two D's of fluids: drug (route and type) and dose. **Route of Administration** will discuss when and how to utilize the various routes of fluid administration available in the horse. As with all drugs, the administration route must be determined early on when developing a fluid therapy plan. In horses, the most commonly utilized routes are intravenous (IV) and intragastric (IG). Rectal (PR) fluid administration may be an alternative and has been a topic of recent interest. Once the route of fluid administration is decided, fluid type and dose must be selected. Information on fluid type and dose for IG and PR fluid administration are provided in **Intragastric Fluids** and **Rectal Fluids**, respectively. Following this, **Intravenous Fluids - Crystalloids** and **Intravenous Fluids - Colloids** will discuss the choice of type and dose of IV fluid therapy, with **Intravenous Fluids - Crystalloids** focused on the crystalloids and **Intravenous Fluids - Colloids** focused on colloids. Throughout this review, we aim to delve into the controversies surrounding choosing the most appropriate route, fluid type, and dose and report the most current literature, in order to help the equine practitioner navigate this territory. Where appropriate, recommendations for treatment of the adult horse will be made, based on the available evidence. It should be noted that the present review does not touch on transfusion medicine, nor parenteral nutrition, information for which has been well-reviewed elsewhere (3–9).

ROUTE OF ADMINISTRATION

Factors that must be taken into account when choosing route of administration include those related to the patient's medical conditions, such as the indications and contraindications for fluid therapy associated with the underlying disease and co-morbidities, as well as non-medical considerations, such as patient temperament, owner finances, and the environment. Together, these determine the likelihood that the treatment will be successful and the potential for adverse effects. **Table 1** provides a starting point for clinicians when choosing a route of administration, while **Table 2** provides common dosing recommendations. Additional details are provided in the relevant sub-sections.

Medical Indication for Fluid Administration

An important first question when choosing the route of administration should be: what is the purpose of fluid therapy? The indications for fluid administration are diverse, but can be generally categorized into emergency resuscitation, replacement of deficits, meeting daily requirements, and targeted treatment of a specific problem. Emergency fluid resuscitation is needed for shock due to decreased effective circulating volume (preload) and circulatory collapse associated with conditions such as severe acute hemorrhage or sepsis. Fluids are also indicated to replace existing deficits, or dehydration. Daily fluid requirements include both maintenance administration to cover expected sensible and insensible losses and to offset ongoing losses. Specific reasons for fluid therapy may include providing nutrients, correcting acid-base and electrolyte abnormalities, diuresis, and, particularly in horses, increasing water content in the ingesta and feces. Although for some indications the choice of route is clear, as is the case for most treatment decisions, more often it is not a black and white or right and wrong answer. For example, IV fluids are a clear choice for resuscitation, but correction of dehydration can be achieved *via* many routes.

Resuscitation

One of the most common reasons for fluid administration is resuscitation of the critically ill patient with insufficient preload due to hypovolemic, distributive, or obstructive shock. These patients require rapid, significant intravascular volume expansion. It should not be surprising that this is best achieved by administering fluids directly into the vascular space (IV). IG and PR routes require absorption and the amount that can be administered as a bolus or over a short period of time is limited. Additionally, in the hypovolemic state, perfusion to the gastrointestinal tract is reduced which slows absorption, further restricting the use of enteral routes for stabilization. Thus, the IV route is the clearly superior method for initial therapy. Once the intravascular volume has been sufficiently expanded and perfusion to the gastrointestinal tract is restored, replacement of deficits with IG or PR may be effective.

Commonly, fluid resuscitation in the equine patient is performed using large volumes of IV isotonic crystalloids, administered as a bolus. Recommendations regarding total dose have varied, although most focus on administration of boluses of approximately 20–25% of a total "shock dose" (80–90 ml/kg for horses) repeated (up to 4–5 times) until indices of perfusion have improved (10). In the horse, the current approach is typically to administer a 10–20 ml/kg bolus of crystalloid followed by reassessment of indicators of perfusion (e.g., heart rate, capillary refill time, pulse quality, extremity temperature, systemic lactate, urination, blood pressure, etc.,), and intravascular volume (jugular fill) (11). In the average 500 kg horse, this bolus would consist of 5–10 L of fluids, which if to be administered rapidly, requires a large (10–14) gauge catheter, wide-bore administration set, and the ability to suspend the fluids from a sufficient height above the horse (10). Alternative methods of volume expansion include administration of hypertonic solutions and/or colloids, as discussed in more detail in **Intravenous Fluids - Crystalloids** and **Intravenous Fluids - Colloids**.

Dehydration

Dehydration is a loss of total body water. In general, more fluid is lost from the extracellular fluid space, and the body preferentially takes fluid from the interstitial space to preserve the circulating volume. In horses, the third space of the gastrointestinal tract serves as a large reservoir of body water accounting for ∼20% of total body water (12, 13). If losses become severe enough,

TABLE 1 | Factors influencing the choice of route of fluid administration to horses.

	Indication/reason for fluid administration				Medical contraindications	Safety	Cost	Patient and environmental factors
	Resuscitation	Dehydration	Daily requirements	Specific problem				
IV	Route of choice	Appropriate choice—may result in rebound dehydration due to continued natriuresis	Appropriate choice	Hypovolemia; significant or rapid ongoing losses; other (e.g., blood product administration, parenteral nutrition, etc.,)	Anuric and oliguric renal failure, caution with heart failure	Catheter associated complications—thrombosis, thrombophlebitis, air embolism	$$$$	Availability for stalling and close monitoring
IG	Unlikely to be of benefit	Appropriate choice—may be preferred due to less urinary loss when discontinued	Appropriate choice	Additional benefits likely for GI hydration; providing nutrients—particularly for enterocytes	Reflux, small intestinal dysfunction (ileus, obstruction), esophageal trauma	Potential for stomach to rupture if small intestinal dysfunction and not properly monitored, epistaxis, esophageal trauma	$	Tolerance of nasogastric tube
PR	Unlikely to be of benefit	Appropriate choice	Appropriate choice	May have additional benefits for small colon impaction	Rectal tear	Limited reports suggest good safety	$	Tolerance of rectal catheter and rate Availability to stall

IV, intravenous; IG, intragastric; PR, per rectum; GI, gastrointestinal.

TABLE 2 | Fluid therapy dosing recommendations for adult horses.

Route	Indication	Fluid type	Dose	Comments
IV	Resuscitation	Isotonic crystalloid	10–20 ml/kg bolus repeated as necessary to stabilize	Used in goal directed fashion with re-assessment of perfusion markers following each bolus. Caution with anuric/oliguric renal failure or heart disease.
		7.2% hypertonic saline	4 ml/kg bolus	Administration must be followed with isotonic crystalloids. Monitoring of electrolytes warranted with prolonged use.
		Hydroxyethyl starches	10 ml/kg/day	Higher rates associated with higher risk of coagulation derangements. Cannot monitor response with TP assessment due to falsely low reading on refractometer.
		Plasma	[(TPdesired – TPpatient)/TPdonor] × 0.05 BW	Monitor for transfusion reactions.
	Maintenance	Isotonic crystalloid	40–60 ml/kg/day	This requirement likely reduced in an adult horse off-feed, although exact requirements in these cases unknown.
IG	Maintenance	Plain water or Electrolyte solution	40–60 ml/kg/day Administered as 4–6 L every 4–6 h or as a constant rate infusion	Typical electrolyte solution recipe: 5.27 g NaCl (table salt), 0.37 g KCl (lite salt), and 3.78 g NaHCO3 in 1 L water. Volumes as high as 8–10 L per bolus reportedly well-tolerated. Volumes over twice maintenance for ingesta hydration not of any additional benefit.
	Fecal hydration	Plain water or Electrolyte solution	Up to 2× maintenance (i.e., 80–120 ml/kg/day) Administered as 4–8 L every 2–4 h or as a constant rate infusion.	
PR	Maintenance	Plain water	5 ml/kg/h *via* constant rate infusion	Plain water reportedly better tolerated than electrolyte solution. Bolus dosing may be tolerated but has not been evaluated in the literature.

IV, intravenous; IG, intragastric; PR, per rectum; GI, gastrointestinal; TP, total protein; PCV, packed cell volume; BW, body weight in kg.

hypovolemia can occur with dehydration and resuscitation would be required. But, if the intravascular volume is successfully spared, correction of the fluid deficit is not an emergency. Thus, treatment can be slower and *via* a variety of routes. In fact, IG and PR routes have been shown to be at least as effective as IV routes for correcting dehydration (14, 15).

Fluid deficits associated with dehydration are estimated based on percent dehydration. Typically, physical exam parameters such as mucous membrane moisture, skin turgor, and relative position of the globe are used when estimating the degree of dehydration, however many of these are unreliable in the horse (16–19). As percent dehydration increases, physical

examination findings that are recommended as indicators begin to include changes consistent with decreased intravascular volume, poor perfusion, and shock such as prolonged capillary refill time, tachycardia, tachypnea, cold extremities, decreased mentation, and poor pulse quality (16). Other clinical indicators of dehydration might include loss of body weight, increased hematocrit and total protein concentrations, or electrolyte and serum osmolarity elevations (17). Bioelectrical impedance has been shown to provide accurate assessment of acute fluid shifts, but is not used clinically (20).

While many publications site specific estimates of dehydration and the expected associated changes in clinical parameters, it is likely that many of these are overestimates based on clinical findings during experimental induction of dehydration in horses. When water is withheld to induce dehydration, variable results have been reported. An older study evaluating 72 h of water restriction resulted in an average of 10.7% dehydration, while 24 h of restriction has resulted in a 3–6.3% decrease in body weight in other studies (14, 21, 22). Although horses in those studies did not experience signs of shock, other studies performed to evaluate the cardiovascular effects of dehydration reported two thirds of horses who were dehydrated to the point of 6.5–7% developed severe neurologic signs, signs of colic, and significant hyperlactatemia consistent with shock (23, 24). These findings suggest that severe dehydration would develop more slowly than duration of disease in many cases presenting with critical illness, and that percent dehydration traditionally considered as moderate can result in severe clinical signs in some horses. The likely overestimation of dehydration based on clinical parameters may be related to the inclusion of parameters associated with shock at higher percentages. It is important to consider that, although dehydration is one potential cause for hypovolemia, diseases associated with critical illness in horses can result in decreased preload through a variety of mechanisms. Thus, these findings are not specific for dehydration and may result in overestimation of dehydration if the underlying disease is more complex.

Daily Requirements

Fluid therapy plans must also account for the daily needs of a patient. Daily fluid requirements for all patients include those required for maintenance, as well as those needed to account for any ongoing losses. All animals have a basal maintenance fluid requirement that must be met in order to cover expected sensible (urine and fecal) as well as insensible (sweat and respiratory) losses. In the adult equid, this requirement is typically reported to be 2–4 ml/kg/h or 40–60 ml/kg/day, although recent work suggests a significant reduction in this requirement when horses are off feed (16, 25). As these maintenance requirements do not necessitate rapid fluid administration, they can be provided *via* routes other than IV, where no contraindications exist. In addition to these needs, any patient that exhibits ongoing losses, such as nasogastric reflux, diarrhea, or third-space losses, will require these losses be replaced in order to maintain normal fluid balance. In some cases, the extent and rapidity of these losses necessitates IV therapy, whereas, in other cases some or all of these losses can be met *via* alternative routes. Importantly, regardless of the route used, all types fluid intake must be considered when making treatment plans – particularly when an animal may be receiving medications, nutritional supplementation, and blood products in addition to their specific fluid therapy.

Specific problems that are treated with fluid therapy include hydration of intestinal contents; provision of nutrition; correction of anemia; treatment of failure of passive transfer; or reduction of cerebral edema, to name a few. Logically, the type and route of fluid therapy required will vary based on these underlying problems. For example, when considering the aforementioned conditions, the practitioner may utilize: IG fluid administration for improving ingesta/fecal water content; parenteral (IV) or enteral (IG) routes to meet nutritional needs; IV administration of whole blood; IV administration of hyperimmune plasma for failure of passive transfer and treatment of specific conditions (e.g., *Rhodococcus equi*, colitis, and coagulopathies); or IV administration of a hypertonic crystalloid or mannitol for cerebral edema.

Medical Contraindications for Fluid Administration

Just as there are specific indications for particular types and routes of fluid administration, there are also specific contraindications. For example, the presence of nasogastric reflux precludes the use of IG fluid therapy, while patients in which venous access cannot be achieved may only be treated *via* enteral routes, and in horses with frequent diarrhea PR fluid therapy may not be worthwhile. The presence of cardiac disease and renal disease can also present challenges in developing a fluid plan. One good example is the patient suffering from cardiac failure who is showing signs of shock from poor perfusion and/or pulmonary edema. Although an IV bolus of fluids would be the most appropriate therapy for other types of shock resulting in poor perfusion, horses with cardiac failure are typically euvolemic or even hypervolemic and would be harmed by large volume resuscitation efforts. In horses with renal disease, it is important to differentiate anuric and oliguric from polyuric disease. While it is easy to volume overload patients that are anuric or oliguric, patients that are polyuric have higher maintenance requirements. Renal disease can also alter the ability to actively remove or retain electrolytes leading to the potential for alterations in sodium, potassium, and calcium, among others.

Safety

As with any other prescription drug, safety is an important consideration when prescribing fluid therapy. Fluid therapy safety issues can be largely divided into those associated with technical and physical aspects of its administration and those associated with incorrect drug choice (fluid type or additives) or dosing (rate of administration).

While IV fluid administration is commonplace, it is perhaps the route posing the highest risk for complications – due to both the requirement for an indwelling IV catheter and the potential for medical errors when selecting and tailoring the fluids themselves. Catheter complications can vary in severity and consequence and may include phlebitis or thrombosis, septic

thrombophlebitis, insertion site abscessation, or acquisition of an air embolus (26). The administration of fluids directly IV means that mistakes in fluid therapy calculations and/or supplementation are likely to be associated with more severe effects, as their uptake cannot be regulated by the intestinal tract in the way that enterally administered fluids might be. Fluid overload is a concept that has, to date, been largely ignored in our adult large animal patients, due to a perceived low risk. However, there has been a recent surge in interest and concern regarding the implications fluid overload might have on disease process and outcomes, particularly related to cases where signs of overload are less obvious. Fluid overload is discussed further in **Rate/Dose of Crystalloid Administration**.

Given the concerns regarding complications associated with IV use in both humans and animal patients, enteral administration has been investigated as a safer route that may also be associated with particular benefits. However, both IG and PR administration are associated with their own potential complications. IG administration requires either repeated passage of a nasogastric tube or the maintenance of an indwelling tube – both of which can be problematic. Repeated passage of a nasogastric tube is often poorly tolerated by the horse and increases the risk for trauma to the nasal passages, ethmoids, and pharynx, and also eliminates the possibility for continuous administration. Maintenance of an indwelling tube, however, can result in pharyngitis, laryngitis, and sinusitis, while reducing the ability to offer free water and feed to horses that might otherwise tolerate it (27, 28). Smaller diameter, softer indwelling tubes may reduce some of these concerns, but are generally more difficult to place and can be challenging to maintain in the authors' experience. Additionally, when administering fluids IG, the practioner must be mindful of the limits of the GI tract. Administration of fluid *via* an IG tube must not exceed the stomach capacity of the horse and, as noted previously, requires a functional proximal gastrointestinal tract. Mixing errors when preparing electrolyte solutions for administration can result in electrolyte and acid base abnormalities and exceeding recommended dosing for $MgSO_4$ as a laxative can result signs of Mg toxicity. While little objective evaluation of the PR administration route exists in horses, some concern has been raised about the type of fluid administered. It has been suggested that hypotonic solutions, such as tap water, may be damaging to the rectal mucosa (29). However, a pilot study performed as part of an experimental study evaluating PR fluid administration found that horses tolerated tap water better than a more isotonic polyionic solution (29). While the reported method of administration *via* a small, soft indwelling catheter is apparently well-tolerated, and considered unlikely to cause significant trauma to the rectum, this cannot be said about other administration devices.

Cost

Sterile, commercially available fluids meant for IV administration in horses, and the materials needed to deliver them, are expensive. While cost varies significantly by location, in the authors' experience, it is not uncommon for the catheter, administration sets, and fluids necessary to administer even just a shock bolus of fluids to be in the realm of hundreds of dollars. In addition to the cost of the actual materials, IV fluid administration requires close monitoring by trained individuals. While some practitioners may feel comfortable with certain clients assuming the risks, this typically requires practitioners to either stay in the field for the duration of therapy, or, more ideally, requires hospitalization – each of which associated with significant cost to the client. In both human and veterinary patients, the move toward enteral fluid therapy has been sought not only because of a perceived improved safety margin and particular benefits for specific problems, but also in large part due to a reduction in workload and cost (30, 31).

In an attempt to reduce the cost of IV fluid therapy in cases where it is warranted over enteral routes, the use of non-sterile, homemade fluids (colloquially also known as "jugs") has been an alternative to commercially available options. These fluids are generally formulated by adding a powdered electrolyte mixture to commercially available reverse osmosis or distilled water meant for human consumption (32). Non-sterile fluids have generally been restricted for use in budget cases or when medical grade fluids have been be in short supply. When commercial alternatives are not available due to shortages, this option seems justified. However, when the only impetus for their use is on the basis of cost, the justification is less clear and legal implications of administering compounded drugs over FDA approved and regulated drugs should be considered. Commercially available fluids are produced in appropriate clean environments and guaranteed to be non-pyrogenic and endotoxin-free, features that cannot be achieved during homemade mixing of potable water, regardless of the source. A recent study compared bacterial and endotoxin contamination in hand mixed non-sterile IV fluids made from chlorinated drinking water and chemical grade electrolytes, compounded IV fluids made from distilled, filtered, irradiated water and filtered electrolyte solution and subsequently autoclaved, and commercially available balanced polyionic fluids (Plasma-Lyte A[1]) (33). This study showed a significant increase and unacceptable level of bacterial contamination in hand-mixed fluids (7/8) compared to compounded (1/8) and commercial (0/8) fluids. The study also detected a low level of endotoxin in 1/8 of the hand-mixed samples and no samples from the other two fluid types. An earlier, small study had suggested significant risk of endotoxin contamination resulting in clinical signs of endotoxemia in non-sterile fluids made using reverse osmosis water and stored in plastic containers (34). A recent retrospective comparing outcomes between horses treated with commercial IV fluids vs. homemade solutions reported no differences in survival to discharge (32). However, the horses treated with homemade fluids reportedly developed more jugular vein complications and hyperchloremic metabolic acidosis while in hospital (32). A similar increased risk for jugular vein complications has been reported in association with non-sterile fluid use in a previous study (35). The hyperchloremic acidosis seen in the study was unsurprising, given the high chloride content (152–153 mmol/L) of all non-sterile fluid formulations (32). The authors of this

[1]Plasma-Lyte A Injection, Baxter Healthcare Corporation, Deerfield, IL, USA.

study described an alternate formulation where some of the potassium was provided as potassium bicarbonate as opposed to potassium chloride, however, the use of this formulation has yet to be evaluated (32).

Patient and Environmental Factors

In addition to the considerations discussed above, sometimes circumstances limit the options available to a patient. Patient temperament can affect the choice of fluid administration route. For example, horses have variable tolerance of indwelling nasogastric tubes and some have a propensity for removing their own catheters. While there are ways to mitigate these issues, if other factors are equal this should be a factor in planning. Where and how the horse is housed can also affect the choice of route of fluid administration. For example, constant rate fluid administration may not be an option in extreme cold due to freezing and rapid IV administration *via* gravity flow requires fluids to be suspended at a significant height. It should be noted that, if facility limitations are likely to negatively impact the standard of care the patient receives, then hospitalization should be considered.

INTRAGASTRIC FLUIDS

IG therapy has a long history of use in equine fluid therapy, with proposed benefits over IV administration that include reduced cost, ease of administration, and improved safety. In addition to these considerations, there is some evidence to suggest that IG administration may be preferable to IV under some circumstances.

Indications for IG Administration

IG fluid therapy should be considered as a route of fluid administration for replacement of dehydration, providing maintenance requirements, and treating specific diseases. While IG administration is a becoming a more commonly utilized route for treating horses suffering from large intestinal impaction, for other equine cases it is frequently overlooked and has been the subject of little research. IG administration of either isotonic electrolyte solution or plain water has been shown to increase fecal water content more effectively than IV fluid therapy (14, 36). Treatment with plain water was shown to result in a rate-dependent improvement in fecal water content when administered at a maintenance fluid rate (50 ml/kg/day), twice times maintenance (100 ml/kg/day), or three times maintenance (150 ml/kg/day) (14). A previous study has reported increased efficacy using balanced electrolyte solution rather than plain water IG or IV fluid administration for right dorsal colon ingesta hydration (36). Lester et al. (14) found that IG fluid therapy in dehydrated horses had a rate-dependent effect on serum osmolality and sodium concentrations, suggesting systemic absorption. These benefits were actually above and beyond those seen in horses administered IV fluids, implying that IG may be a very effective route for rehydration (14). Two retrospective studies have reported positive outcomes in treatment of large colon impactions with IG fluid administration (37, 38).

Similar benefits of oral rehydration therapy have been documented in humans. In children, oral rehydration has become the recommended first line therapy for mild and moderate dehydration (30, 31, 39). Initial studies in horses evaluating rehydration after exercise supported the use of oral rehydration solutions for restoration of circulating volume after exercise (40, 41). These studies evaluated several indirect indices of circulating and total body water volume (i.e., plasma volume, changes in total protein, body weight) following rehydration with plain water or an isotonic oral rehydration solution *via* nasogastric tube (40, 41). They reported evidence of changes in circulating volume despite small volume (4 L) administration, and that an isotonic oral rehydration solution appeared more efficacious than water, although both appeared safe (40, 41).

Interestingly, despite the evidence, there continues to be a tendency to rely on IV fluid therapy in people and equine practice based on similar arguments: perceived ease of use and more rapid patient response, as well as the expectations of clients and referring clinicians (39). The authors suggest that, provided the horse has a functional proximal intestinal tract, evidence supports IG fluid administration as an easy, inexpensive route of administration for systemic and gastrointestinal hydration.

Types of Fluid for IG Administration

The most appropriate solution for IG administration remains a topic of debate. In human medicine, there is a general acceptance that an electrolyte rehydration solution, rather than plain water, should be utilized and, in almost all cases, these solutions include a glucose or dextrose source (30, 31, 39). Additionally, most human formulations also contain some buffer component – most commonly bicarbonate or citrate.

The theory behind using an electrolyte solution rather than water relates to the net effect this will have with respect to subsequent fluid shifts. When plain water is administered, it will be absorbed and equally divided between the extracellular fluid space (one fourth of which is in the intravascular space). The extracellular fluids will then be relatively hypotonic and further redistribution into the intracellular fluid space will occur to balance tonicity between these compartments. By comparison, if an isotonic electrolyte solution is administered, the fluid will once again be initially taken up and equally divided between the extracellular fluid spaces. However, there will not be the osmotic drive to initiate further redistribution intracellularly, and therefore more of the absorbed fluid will remain in the extracellular (and, thus, intravascular) space. Although plain water and electrolyte solutions increase gastrointestinal water content and plain water has been shown to correct dehydration in horses, concerns have been raised regarding the hypotonicity of plain water resulting in the possibility of serious electrolyte abnormalities (36). However, no clinical signs were reported in relation to the mild hyponatremia in a one study, and a second investigating the use of plain water reported no complications with its use (14, 36). Evaluation of horses administered furosemide and then exercised to induce dehydration found that consumption of salt water resulted in more fluid intake and body weight gain in the first 1 h compared to plain water (42).

The purpose of the glucose/dextrose component in human rehydration solutions is to drive glucose cotransport of sodium within the intestinal tract, ultimately creating more solvent drag and fluid uptake. Interestingly, however, several studies in horses have not supported their use over a electrolyte solution not containing glucose (43, 44). Ecke et al. (45) investigated the use of a glucose -based rehydrating solution commonly used in diarrheic calves for treatment of adult horses with experimentally induced diarrhea. They concluded that it was not effective for this purpose, and in fact precipitated acid-base and electrolyte derangements (45). More recently there has been a shift toward polymer-based rehydration solutions that contain starch components rather than glucose or dextrose. The aim of these solutions is a slower, more sustained glucose release and less abrupt increases in intra-luminal glucose, which may actually act counterproductively by creating an osmotic drag into the gastrointestinal lumen and net loss of fluids (31). To the authors' knowledge, such polymer-based oral rehydration solutions have not been used in equine patients.

The buffering component of human rehydration solutions is included in an attempt to counteract metabolic acidosis, particularly in diarrheic patients. Many of the oral rehydration solutions used in the horses do include sodium bicarbonate in varying proportions (e.g., 5.27 g NaCl (table salt), 0.37 g KCl (lite salt), and 3.78 g NaHCO3 in 1 L tap water) (16). However, a comparison of sodium chloride solution to a more complete buffered electrolyte solution has not been performed in studies of experimental dehydration to the authors' knowledge. The authors are also unaware of any studies evaluating the use of buffered solutions for either voluntary consumption or IG administration in horses with diarrhea, although some clinicians will provide horses with the choice of electrolyte water clinically.

Methods and Rates of IG Fluid Administration

Intragastric fluids can be administered either as a bolus or as a continuous infusion *via* nasogastric tube. Bolus dosing can be convenient, as it does not require a stall set-up that allows for a continuous administration. With gastric emptying times for fluid reported at around 15 min, frequent boluses of appropriate volumes should be possible and well-tolerated, so long as normal small intestinal function is adequate (46). However, there is a limit to how much can be administered at any one time given the capacity of the stomach, the maximum of which has been reported to be approximately 15–18 L in the average adult horse (47). Interestingly, Lester et al. (14) were able to administer up to three-times maintenance over four treatments, which, based on the weights in their population would be as much as almost 20 L at each interval. Despite administering more than the reported capacity of the stomach, they reported being able to administer this over 15 min with no ill effects (14). Monreal et al. (37) similarly describe administration of volumes as high as 8–10 L every 2 h, with no signs of discomfort attributed to this treatment. In the authors' experience, it is better tolerated to administer smaller volumes more frequently, such as 4–6 L of fluids every 2–4 h. If administering as a constant rate infusion, a rate of 1–2 L per hour has been recommended (15).

RECTAL FLUIDS

Rectal fluid administration has gained recent interest within equine practice as an attractive alternative because of the ability to administer relatively large volumes with very little cost. Use of this route precludes the requirement for sterile fluids, and the need for precise tailoring of the fluid balance. While rectal fluid therapy has been reported in other species, including humans, studies in horses have been limited to date (48–52).

Types and Rates of Fluid Administration PR

The first study the authors can identify evaluating PR fluids in horses was performed in 1979 evaluating administration of saline PR. In that study, 44 L of saline were administered to horses with furosemide-induced dehydration (53). An acidifying effect of the saline was observed (see **Balanced Polyionic vs. Saline** for more on the potential detrimental effects of saline), but no effect on hydration was identified. A separate part of this study evaluated how far orally fluid migrated in horses and found it rarely reached the level of the pelvic flexure (53). More recently, a letter to the Veterinary Record reports briefly on one practitioner's use of PR fluid administration and two studies have been performed in horses evaluating PR fluids - one small study in horses with naturally occurring mild dehydration and another experimental study comparing IV, IG, and PR fluids in healthy horses (15, 29, 54).

A 2018 study evaluated PR therapy in eight horses with naturally occurring mild dehydration (6% estimate based on clinical signs). Horses that were deemed to be mildly dehydrated, based on loss of body weight and evidence of hemoconcentration, were administered their calculated fluid deficit of a homemade polyionic solution PR in boluses of no more than 5 L at a time. The procedure was well-tolerated and resulted in a measurable improvement in hematocrit and total protein concentrations, with minimal changes in overall electrolyte balance (15).

A 2019 study evaluated both the tolerance of equine patients to rectally administered fluids, as well as the resulting effect on clinical chemistry changes in an effort to confirm absorption (29). An initial pilot study was performed in order to determine the most appropriate type (polyionic solution or plain tap water) and rate of administration (2.5, 5, 7.5, and 10 ml/kg/h) of fluid to be used in the main study. Due to less tolerance of polyionic fluids and higher rates during the pilot study, the horses were subsequently administered plain tap water at 5 ml/kg/h (roughly 2–2.5 times maintenance rate) *via* continuous gravity flow over the course of a 6-h period. In the main randomized, crossover study, six horses were treated with each of 3 fluid therapy treatments (polyionic solution IV, polyionic solution IG, or water PR at a rate of 5 ml/kg/h) and a control treatment where no fluid was administered. Results indicated that horses administered tap water per rectum at these rates tolerated this well and exhibited evidence of hemodilution (based on decreased PCV/TS) similar to that achieved *via* the IV and IG routes (29). The authors concluded this to be both a safe and effective means by which to

either replace or augment other routes of fluid administration. It should be noted, however, that the effects of administering hypotonic tap water on the rectal mucosa was not evaluated.

Methods for PR Fluid Administration

In the more recent equine reports, PR fluids have been administered *via* gravity flow through either a small, well-lubricated esophageal tube passed 10–15 cm into the rectum or a small (24 Fr) soft enema tube (15, 29, 54). In the authors' experience, placement of a long foley catheter or red rubber catheter has been well-tolerated. Placement of a single interrupted suture between the edge of the catheter and the anus or perineum has been beneficial in keeping the catheter from falling to the ground if displaced, as has been seen to occur with higher fluid rates or defecation.

INTRAVENOUS FLUIDS - CRYSTALLOIDS

Crystalloid fluids are the mainstay of IV fluid therapy, both in human and veterinary medicine. Much debate has developed with respect to the best type and rate of crystalloid administration.

Types of Crystalloids

Crystalloids can be defined based on their tonicity, use, and/or electrolyte composition. Most crystalloids are isotonic, meaning that they have a similar tonicity to fluid within the body, both intra- and extra-cellularly. Sodium is the main determinant of solute concentration and, therefore, osmolarity in extracellular fluids within the body and in IV fluids. Thus, low sodium fluids are hypotonic unless a solute, usually dextrose, is added and high sodium fluids are hypertonic. Most commonly, low sodium fluids fall into the category of fluids used to maintain total body water (fulfill daily fluid requirements). High sodium, hypertonic solutions, are most frequently utilized to rapidly shift fluids into the intravascular space during resuscitation and can also be useful for treatment of cerebral edema. Correction of sodium imbalance is another indication for administration of hypo- or hyper-tonic (low or high sodium) fluids. The distinctions between most commonly available commercial crystalloid solutions are discussed below. In addition to these basic crystalloid options, some additional alternatives exist, such lactate-rich polyionic solution and bicarbonate solutions, which have specific purposes related to restoring circulating volume or normalizing acid-base disturbances (55, 56). Modification of the common commercial solutions with additives is also commonplace to address electrolyte and acid-base imbalance and supplement nutrients.

Replacement vs. Maintenance

Replacement fluids are designed to "replace" deficits, generally those associated with hypovolemia and dehydration. Maintenance fluids are designed to "maintain" homeostasis by providing requirements associated with maintenance needs and expected losses. Because the deficits being replaced in cases of hypovolemia (intravascular) and dehydration (preferentially interstitial) involve the extracellular fluid space primarily, replacement fluids have a composition similar to extracellular fluid—high in sodium and chloride, low in potassium, calcium, and magnesium. In contrast, the losses being addressed with maintenance fluids are lost from both intra- and extra-cellular fluid spaces through fluids such as urine, which are generally comparatively low in sodium and chloride and high in potassium, calcium, and magnesium. Thus, maintenance fluid composition is closer to total body water electrolyte composition. The low sodium concentration of maintenance fluids makes them hypotonic unless dextrose is added.

Commercially available replacement fluid options available include: 0.9% sodium chloride (0.9% NaCl)[2], lactated Ringer's solution (LRS)[3], Normosol-R[4], Plasma-lyte A[1], and Plasma-lyte 148[5] (11). Commercially available maintenance options include: Normosol-M[6], Plasma-lyte 56[7], 2.5% dextrose in half-strength saline (0.45% NaCl + 2.5% dextrose)[8], and 5% dextrose in water (D5W)[9] (17). While clearly a variety of options exist, the reality is that most clinics only stock one and at most a few options in sizes appropriate for use in adult horses. When a single fluid is stocked, in general it is a replacement fluid, as these are available in large sizes, are most commonly used, and can be given rapidly to patients in need of resuscitation. However, given the electrochemical makeup of these fluids, maintaining patients on this type of fluids, beyond the initial replacement period, inevitably results in sodium loading and inadequate replacement of other electrolytes. While potassium, magnesium, and calcium can be supplemented in replacement fluids, without dilution of the base fluid, the sodium load remains an issue.

Such a significant sodium load results in natriuresis and thus diuresis, which is logically counterproductive and can result in depletion of additional electrolytes. In the study by Lester et al., kaliuresis and diuresis persisted in the recovery period following administration of IV polyionic replacement fluids. Horses in the IV treatment group were unable to completely restore hydration during the treatment period and illustrated a rebound dehydration during the 24 h following treatment (14). Similar incomplete rehydration was reported in an earlier study using saline for rehydration in horses (57).

Sodium that is not able to be excreted contributes to fluid retention and predisposes to fluid overload and development of edema. The general approach to fluid therapy in adult equids has been to consider them relatively tolerant of overzealous fluid therapy efforts in comparison to their small animal counterparts, due in large part to the comparatively fewer cases of cardiac dysfunction or renal insufficiency. However, in the diseased adult patient or neonate with less tolerance for large sodium shifts, the

[2]Saline Solution 0.9%, VETone, Boise, ID, USA.
[3]Lactated Ringer Injection, Aspen Veterinary Resources Ltd, Liberty, MO, USA.
[4]Normosol-R, Hospira Inc, Lake Forest, IL, USA.
[5]Plasma-lyte 148 Injection, Baxter Healthcare Corporation, Deerfield, IL, USA.
[6]Normosol-M & 5% Dextrose, Hospira Inc, Lake Forest, IL, USA.
[7]Plasma-lyte 56 & 5% Destrose Injection, Baxter Healthcare Corporation, Deerfield, IL, USA.
[8]Veterinary 2.5% Dextrose & 0.45% Sodium Chloride Injection, Zoetis Inc, Kalamazoo, MI, USA.
[9]5% Dextrose Injection, Baxter Healthcare Corporation, Deerfield, IL, USA.

potential for sodium and fluid overload should be acknowledged and avoided.

Balanced Polyionic vs. Saline

A recent controversy within crystalloid fluid therapy is the shift away from using 0.9% NaCl as the replacement fluid of choice in favor of a more balanced electrolyte solution. Historically, saline has been the mainstay fluid of choice in human medicine due to the perception that it is the most physiologically appropriate choice. However, this has been questioned due to concerns regarding the effects of increased chloride load from its administration (58–60).

Physiologic 0.9% saline, or normal saline, contains sodium and chloride only, and each of these components exists in higher levels in this fluid than is present in normal equine plasma (154 vs. ∼130–140 mmol/L for sodium and 154 vs. ∼90–100 mmol/L for chloride) (11). Normal saline administration thus results in a high sodium burden, which stimulates natriuresis which may be counterproductive in patients suffering from hypovolemia or dehydration. A potentially larger concern regarding the use of normal saline, however, is associated with the high chloride burden following administration. This has been shown to consistently result in a hyperchloremic metabolic acidosis – hence the common description of saline as an "acidifying fluid." This effect on acid-base balance can be explained in the context of strong ion difference, as the increase in chloride load results in a decreased strong ion difference, a decrease in bicarbonate and base excess as a result, and ultimately a reduction in blood pH. In patients already suffering from acid-base disturbances, this may be particularly contraindicated. A study in endurance horses comparing saline to acetated polyionic fluids showed a decrease in sodium-chloride difference consistent with the potential for a hyperchloremic metabolic acidosis in horses administered saline (60). Furthermore, saline use in both healthy and critically ill humans has been shown to result in an increased risk for renal compromise, thought to be explained by a chloride-mediated renal vasoconstriction and subsequent reduction in renal perfusion (58, 59, 61). Despite these concerns, a large Cochrane review evaluating 21 randomized controlled studies and three ongoing studies was unable to identify an improved mortality in human critically ill adults or children treated with a buffered solution vs. normal saline (62).

While a balanced electrolyte solution is favored for the majority of equine patients, there are certain disease states in which sodium chloride would be preferable. The first of these is logically patients with a hypochloremic metabolic alkalosis, as the propensity for a hyperchloremic metabolic acidosis may actually be of benefit in correcting this disturbance. Normal saline has also generally been selected preferentially over balanced electrolyte solutions in hyperkalemic patients. This is because all balanced electrolyte solutions contain some potassium, which may theoretically worsen the hyperkalemia. However, the acidosis induced by high chloride fluids induces a shift of potassium out of cells which may increase potassium to a greater degree than lactated ringer's solution (63, 64). Lastly, sodium chloride is considered superior in cases of head trauma, as it is thought that the relative hypotonicity of balanced electrolyte solutions may result in fluid shifts that could result in increased intracranial pressure (59).

Hypertonic Saline

Most commonly hypertonic saline is available as a 7.2% solution[10], with sodium content of 1,232 mOsm/L, resulting in almost nine times the tonicity of plasma (65). Administration of this hypertonic solution results in significant and rapid fluid shifts into the intravascular space, initially from the other extracellular compartments (i.e., interstitial space) and will continue from the intracellular space. As a result of these fluid shifts, the effective expansion of circulating volume is in the order of 3.5 times the administered volume (11). Despite such a rapid initial expansion, this effect is relatively short lived, due to redistribution of electrolytes and water across the vessel wall as expected with all IV crystalloid administration. Thus, for a sustained effect and, to avoid ill-effects of intracellular dehydration, hypertonic saline administration should be followed by larger quantities of IV isotonic replacement crystalloids. Administration of enteral fluids may provide an alternative to IV isotonic replacement crystalloids following hypertonic saline resuscitation. In calves with diarrhea and moderate dehydration and acidosis, small volume IV hypertonic saline followed with oral electrolyte solution was effective at rapidly improving hydration and acid-base status (66).

The rapid volume expansion achieved with hypertonic saline administration makes this an excellent choice in the resuscitation of the hypovolemic patient. In an experimental study in which anesthetized horses underwent controlled exsanguination to achieve induced hemorrhagic shock, administration of hypertonic saline resulted in rapid plasma volume expansion and urine output, along with sustained elevations in numerous cardiovascular parameters including cardiac output, stroke volume, mean arterial pressure, and contractility (67). Comparatively, administration of an isotonic saline solution only resulted in transient increases in mean arterial pressure but no changes in other cardiac parameters, plasma volume, or urine output (67). These rapid fluid shifts are also of benefit in patients suffering from life-threatening increased intracranial pressure and/or cerebral edema, as a means of reducing the intracranial volume. Other purported benefits of hypertonic saline include anti-inflammatory, anti-edema, and potential inotropic effects, although the last of these is difficult to separate from its volume expanding effects (11). Obvious contraindications exist, such as the already severely hypernatremic patient (unless the need to treat of cerebral edema supersedes this), as well as in patients with uncontrolled blood loss where the increase in circulating volume and inotropic benefits may actually be problematic.

Rate/Dose of Crystalloid Administration

The rate of crystalloid administration is typically dictated by the indication for the fluid therapy. However, as briefly discussed above, to date there has often been an inclination to treat with very aggressive fluid therapy rates, especially for particular problems such as intestinal impactions. In

[10]Hypertonic Saline 7.2%, VETone, Boise, ID, USA.

addition to the concerns regarding high fluid rates resulting in counterproductive diuresis (particularly with high sodium content of replacement fluids commonly used in equine practice), other potential drawbacks of this approach include cost, lack of actual benefit, and the potential for detrimental fluid overload.

Interestingly, studies evaluating the use of IV fluids to improve fecal water content have been conflicting. Lester et al. (14) identified that rates of 100–150 ml/kg/day (∼2–3 L/h or 2–3 times maintenance) did increase fecal water content, although there was no additional benefit of the higher rate over the lower. In contrast to this, Lopes et al. (36) found that rates as high as 5 L/h had no effect on the hydration of colon contents or feces. The difference in the results of these two studies may be related to the hydration status of the horses and, therefore their gastrointestinal contents, when fluids were administered. This suggests that extrapolation to clinical patients with highly variable diseases is unlikely to be straightforward and further investigation is needed. However, while IV fluid therapy may be of benefit in gastrointestinal hydration, the concept of aggressive "overhydration" is not supported by current literature and the effects of combining enteral and IV therapy is unknown.

As noted, the concept of fluid overload, a commonly considered issue in human and small animal medicine, has been largely ignored in treating the adult equine. Although, few adult horses suffer from cardiac or chronic renal disease predisposing to fluid overload, other risk factors of hypoproteinemia and systemic inflammation are frequently found in the critically ill equid. Additionally, many of these same patients are at risk for acute kidney injury and compromised renal function. In human medicine, aggressive fluid therapy in both the perioperative and intensive care settings has been associated with the development of fluid overload and subsequent ill-effects including interference with gas exchange due to the development of pulmonary edema, impaired wound healing, compromised renal function, and increased mortality in septic and post-operative patients (2, 68). As a result, there has been a shift toward a more tailored fluid therapy approach that is adjusted in relation to the patient's status and response and a focus on de-escalation, and even evacuation *via* diuretic therapy, when appropriate (2, 68). An additional consequence of fluid overload in people that is of particular interest to equine practitoners is the negative impact of fluid overload on gastrointestinal healing and post-operative function. It been theorized that aggressive peri-operative fluid therapy can result in subsequent gastrointestinal wall edema which may contribute to poor gastrointestinal function and post-operative reflux (POR) (69). Studies of restricted fluid therapy have shown this to be associated with a decreased risk of ileus and improved outcomes in human patients (70, 71). Further to this, electrolyte abnormalities, which can be induced by aggressive fluid therapy, are known to contribute to POR in other species, further supporting re-evaluation of the fluid approach in these patients (71, 72). One study evaluating the influence of both total fluid volume and electrolyte derangements on the incidence of POR in horses did not identify either of these as factors contributing to the development of POR (69). However, this was a single study that was retrospective in design and did not have a means for accurate and consistent measure of fluid balance. Furthermore, most fluid rates reported in this study would not have been classified as aggressive based on human medical standards, which are commonly on the order of 240–440 ml/kg/day, vs. the 102–117ml/kg/day reported here (69). Thus, further investigation is warranted. In the meantime, monitoring for fluid overload in all critical patients is probably indicated. While quantitative monitoring of "ins and outs" is difficult, monitoring for indirect signs such as significant weight gain or development of peripheral edema is easy to do. Central venous pressure as a method to evaluate intravascular volume has been evaluated in horses, but clinical use is difficult due to inconsistent results associated with technical errors and potential for effects of confounding diseases/conditions.

INTRAVENOUS FLUIDS - COLLOIDS

Colloids can be broadly grouped into two types: natural and synthetic. Natural colloids include whole blood, plasma, and albumin, while synthetic colloids include hydroxyethyl starch (HES) solutions, dextrans, and gelatins. Hetastarch[11] is the most widely used and available HES, but other formulations including Pentastarch[12] and Tetrastarch[13] can be found and have been evaluated. The different formulations of HES solutions vary in molecular weight, substitutions, and carrier solution. While previously considered an important component of the stabilization and treatment of the critical care patient, colloids have seemingly fallen out of favor in both human and veterinary medicine. Much of the decrease in use is related to the controversies surrounding potential harmful effects, particularly in patients with critical illness, specifically sepsis and burns, and the resulting regulations in Europe related to the use of HES. This began in late 2013, when the European Medical Agency stated that HES should not be used for patients with sepsis, burns, or critical illness, in response to the results of several landmark studies showing increases in mortality and requirement for renal replacement therapy in septic patients (73–75). The recommendations did allow for continued use for the treatment of acute hemorrhagic shock if crystalloids were not considered sufficient, for no more than 24 h and with kidney monitoring. Further, study was recommended for elective surgery and trauma patients. In 2018, the committee voted to suspend HES from the European market due to evidence of continued use of HES off label in septic patients (76). The vote was fairly close (15–13) and there are a number of correspondences and editorials that are against the ban (77, 78). Those in favor of continued use point to positive results in some studies, lack of consistent support of negative effects in multiple studies, and the ongoing clinical studies evaluating safety for elective surgery (PHOENICS (NCT03278548)) and trauma patients (TETHYS (NCT03338218)) (79–83). There are also concerns for the potential to worsen outcomes in conditions that benefit from HES, particularly in regions where alternatives are limited.

[11] 6% Hetastarch, Hospira Inc, Lake Forest, IL, USA.
[12] Pentaspan, Bristol-Myers Squibb, Montreal, QC, Canada.
[13] Voluven, Fresenius Kabi Norge AS, Halden, Norway.

Colloid Osmotic Pressure and the Proposed Role of Colloids in Health and Disease

Colloids are relatively large, charged, osmotically active molecules. The amount of osmotic pressure created by colloids in a solution is measured as colloid osmotic pressure and also known as oncotic pressure. The number of molecules, rather than their size, is responsible for the osmotic pull. For this reason, in plasma, it is albumin, not globulin, that is the predominant molecule responsible for oncotic pressure, because there are more molecules of albumin. It is for a similar reason that smaller molecular weight HES solutions should provide more volume expansion that larger molecular weight HES. Due to the large size and charge of colloid molecules, normal vessels are not permeable to colloids, which is in contrast to other osmotically active molecules such as electrolytes and glucose. Whereas, electrolyte and glucose concentrations quickly equilibrate between the plasma and interstitial spaces, colloids remain within the vascular space, maintaining an osmotic gradient that encourages transcapillary movement from the interstitium to the intravascular space and keeps water in the vasculature, providing a more sustained intravascular volume expansion (84, 85).

The underlying principle behind the use of colloid therapy to produce sustained volume expansion was the standard Starling equation of transcapillary movement. In summary, the equation states that the direction and amount of transcapillary fluid movement is related to the balance of hydrostatic and colloid osmotic, or oncotic, pressures between the capillary and the interstitium and a factor representing the permeability of the vessel wall (K_f). If applied to crystalloid administration, the addition of isotonic fluids within the vascular space results in an increased volume and, therefore, hydrostatic pressure along with dilution of colloid/protein and, therefore, a decrease in oncotic pressure within the vessel. Both changes in the capillary favor a net movement of fluid into the interstitium. If applied to colloid administration, the increase in volume still results in an increase in hydrostatic pressure, but the increase in colloid results in an increase in oncotic pressure within the vessel, pulling fluid into the vessel. The goal is to increase the oncotic pressure enough to offset and outweigh the increased hydrostatic pressure to favor net movement of fluid from the interstitium and into the intravascular space. Thus, theoretically colloid administration should result in a more significant volume expansion effect for a given volume administered, with less redistribution of the fluid to the interstitium, providing a more sustained expansion and minimizing the negative effects of accumulation of interstitial fluid.

While this is a fairly straightforward concept to understand, the accuracy of the Starling equation when applied clinically has been called into question, creating doubt about the expected response to colloid administration in critical patients (86, 87). Two main problems exist with this concept as it currently stands: there is evidence to suggest that the interstitial space and its fluid balance changes in disease states; and the lining of the microvasculature may not allow the movement of fluid from the interstitium back into the vasculature as once thought (86, 87). With respect to the first of these, it has been shown that inflammation and other pathology can result in negative pressure within the interstitium, promoting transcapillary movement of fluid into this space and subsequent edema formation (88). The thought is that an increase in the plasma oncotic pressure would not necessarily overcome the vacuum-like draw of fluid into the interstitium and thus fluid accumulation would result. Further compounding this, the endothelial glycocalyx, which is the region of the vessel thought to regulate the movement of fluid between the vasculature and the interstitium, is proposed to limit the reuptake of fluid from the interstitium back into the capillaries (86, 87). This would mean the proposed benefit of added volume expansion following colloid administration is unlikely. Additionally, any fluid lost to the negative space of the interstitium may be trapped, especially if leaky vessels (increased K_f) allow colloids to accumulate, along with the water they attract (86, 87). Smaller colloid particles (lower molecular weight HES, for example) are more likely to leak out of even normal vessels.

Indications for Use of Colloids

The indications for colloid administration relate to the proposed role of the colloid osmotic pressure exerted by colloids in the fluid balance between the intravascular and interstitial spaces. Overall, administration of colloids intravenously is generally performed with one of two goals: improving colloid oncotic pressure (COP) or inducing more rapid and sustained volume expansion than crystalloids during fluid resuscitation of critically ill patients (89). Related to these goals, colloid administration has been suggested for treatment of two main pathologies: conditions resulting in decreased colloid osmotic pressure, such as protein losing enteropathy, and conditions requiring rapid expansion of intravascular volume. In addition to these indications for colloids as a whole, natural colloid options such as whole blood or plasma are often administered for a particular purpose in certain cases – such as replenishing red cells, plasma proteins, and coagulation factors in the case of whole blood, or for anti-endotoxic or coagulation benefits in the case of plasma. As the focus of this review is not transfusion medicine, the authors direct the reader to available literature on the uses, purported benefits, and drawbacks of these products (3–5, 90–94).

Despite the theoretical benefits of colloid administration, results of clinical studies have failed to consistently show advantages over crystalloids in human medicine (84, 85). Initial clinical studies in people did report significantly improved outcomes in critically ill patients who received colloid-based volume resuscitation in comparison to crystalloids (84). However, many of these publications have been discredited, and this has subsequently muddied the water with respect to the meta-analyses in which they were included (84). It seems likely that consideration of the underlying disease is important when assessing both the benefit and risk of colloid administration. Patients with critical illnesses like sepsis and burns have shown minimal to no benefit and there is evidence of worsened outcomes and side effects when treated with colloids when compared to crystalloids (95). In contrast, patients with hypovolemic shock, trauma, and undergoing elective surgeries

may experience benefits and even those at risk for kidney injury may not have an increased risk of renal complications (79–81, 95). While there is some support for their use in equine patients, there has been no strong evidence for an overall improvement in outcome.

In general, regardless of the type, colloid products are more costly than crystalloid alternatives, when compared on a volume basis (85). However, if increasing the COP results in maintenance of fluid within the vascular space and decreased redistribution of crystalloids to the interstitial space, the end result could be reduced edema formation and requirement for crystalloid administration. This could potentially have the effect of reducing overall cost.

Improved Colloid Oncotic Pressure

With respect to improved COP, administration of synthetic colloids to healthy horses and ponies in an experimental setting has been shown to result in an increase in oncotic pressure for as long as 24 h post-administration (89, 96). When comparing the improvement in COP following administration of a synthetic colloid (Hetastarch or HS) and plasma to healthy horses, McKenzie et al. (97) reported a similar increase, regardless of the colloid used. Interestingly, despite its frequent use in anesthetized horses in an attempt to counteract the decreased COP seen under anesthesia, the effects of synthetic colloids in these settings is variable (98–101). A study comparing the effects of HS to isotonic crystalloids on COP in healthy patients undergoing elective surgery found higher COP following the colloid administration (101). In contrast, another study performed in a similar population compared the effects of isotonic crystalloid to a combination of crystalloid with synthetic colloid (HS) and found no difference in COP between the groups (100). When evaluated in critically ill horses suffering from hypoproteinemia secondary to gastrointestinal disease, synthetic colloid administration was shown to result in a significantly increased oncotic pressure (102). While administration in this study resulted in an ∼20% increase in COP, no horses were seen to have a return of COP to that measured in healthy horses (102). A more recent retrospective study comparing outcomes in horses with enterocolitis treated with plasma to those treated with a synthetic colloid (HS) reported significantly better outcomes in the plasma treated horses (80 vs. 27% survival) (103). It should be noted, however, that another retrospective study published the same year reported that horses who had received a plasma transfusion for treatment of typhlocolitis/colitis had a higher odds of dying than non-transfused horses (90). The retrospective nature of this study makes it impossible to identify whether this was due to more severe disease in the transfused patients, as well as the reasoning behind the use of plasma in each particular case (i.e., low total protein, coagulation concerns, etc.,), making the interpretation of these findings particularly challenging (90).

Use in Fluid Resuscitation

While the colloid literature in human medicine has focused a great deal on outcomes (albeit with much controversy over the legitimacy of the results), similar studies within the equine literature are sparse. Several studies have evaluated the effect of colloid administration on hematologic parameters that are considered indicative of hemodilution, supporting the premise that these products enhance the circulating fluid volume. Previous reports have indicated that both synthetic colloid and natural colloid options reduce hematocrit (HCT) or packed cell volume (PCV) and/or total protein (TP) or total solids (TS) concentrations in healthy horse (89, 97, 100, 101, 104). A report from Epstein et al. documented an increase in systemic blood pressure following administration of HES products, while another by Ohta et al. documented an increase in cardiac output (despite failing to identify an increase in blood pressure), further supporting their role in resuscitation (89, 105). However, in an experimental study of anesthetized horses given endotoxin, resuscitation with hypertonic saline and HES did not reverse the negative cardiovascular effects of endotoxemia (106). Albumin, a natural colloid commonly used in people and with some frequency in small animals, was recently evaluated for its volume expansion effects in horses (107). Administration of an equine albumin product resulted in a reduction in HCT and TP, improved mean arterial pressure, and shorter capillary refill time (107). Clearly, while the influence of these products on outcome has yet to be fully elucidated, these findings suggest a plausible role in resuscitation of the equine patient, particularly when faced with a case refractory to other treatments.

Side Effects of Colloids

Recent reports in the human literature have brought to light concerns regarding the potential for complications following synthetic colloid use. In conjunction with the now limited reliable data supporting their use, this has led to a significant move away from their use in human medicine (85). The primary side-effects seen in people that have been discussed to date include: allergic-type reactions, accumulation in the tissues; renal compromise resulting in an increased need for renal replacement therapy; and coagulation derangements resulting in a need for blood transfusion (85). Both renal and coagulation side effects may be more likely with larger molecular weight HES solutions associated with clogging glomeruli and interfering mechanically with coagulation.

In veterinary species, side-effects of colloid administration have not been well-studied. There appear to be no reports of hypersensitivity reactions and tissue accumulation. However, there has been some evaluation of their renal and coagulopathic consequences. Administration of HES did not appear to increase the risk of acute kidney injury according to one study in cats, but the two studies in dogs have divergent outcomes related to risk associated with HES administration (108–110). Changes in coagulation have been documented *in vitro* in cats and in dogs with naturally occurring hemoperitoneum (111, 112).

While there is a paucity of research regarding other sequelae following their use in horses, there is some support for changes in coagulation parameters following synthetic colloid administration (89, 104). The previously reported effects of synthetic colloids on coagulation have been attributed to both a dilutional effect and an interference with platelets, clotting factors, and the fibrinolysis system (113, 114). Based on findings reported in people, Epstein et al. evaluated the effects of

two formulations of HES products – hetastarch (HS) and tetrastarch (TS) - as well as normal saline, on various hemostatic parameters in healthy horses (89). The study identified a variety of statistically significant changes in coagulation testing. It should be recognized that most changes were mild, with values often remaining in the normal range and unlikely to be clinically significant. It was found that all three solutions resulted in a transient decrease in platelet count and activated clotting time, as well as a transient increase in prothrombin and activated partial thromboplastin times (PT and aPTT, respectively). Interestingly, aPTT was higher in horses receiving HS vs. TS. Platelet aggregation was also altered in response to colloid therapy, with automated platelet function testing closure times prolonged in both colloid groups, again more so with HS than TS. Another study performed by Vilojen et al. evaluated the hemostatic effects of TS administered at varying doses (10, 20, and 40 ml/kg) in healthy horses (104). All thromboelastography (TEG) values remained within normal limits in all groups throughout the study. However, the higher dose used was considered more likely to induce measurable changes in TEG parameters. While neither of these studies were performed in clinical patients and no clinical bleeding abnormalities were reported, they do seem in line with coagulation derangements seen in other species. In contrast to these studies, no alterations to coagulation were identified following administration of hypertonic saline and HES to horses administered endotoxin under general anesthesia (115). Additional work is needed to evaluate these effects in clinical patients, particularly those more likely to be at risk for pre-existing thrombocytopenia, thrombocytopathia or coagulopathy.

CONCLUSIONS

It is clear that, despite its frequent use, the most appropriate way in which to utilize fluid therapy is far from well-understood. Review of the literature suggests that many of the issues that plague equine clinicians mirror those encountered in human medicine. However, while multiple experimental studies have been performed, the equine literature is severely lacking in large-scale, well-designed studies in the clinical patient. This significantly limits the ability to provide practitioners with evidence-based recommendations for fluid therapy in horses. Based on the review of the present literature in horses and extrapolation from literature in other species the following basic summary points can be made:

1. IV fluid therapy remains the most appropriate route for volume resuscitation, however, IG and PR fluid administration are efficacious and seemingly safe routes for correcting and maintaining systemic hydration and increasing fecal water content at rates that have been reported in the literature.
2. Aggressive IV fluid rates (greater than twice maintenance) are likely to be no more effective at increasing fecal water than lower rates, despite significantly increasing the cost and increasing the risk of electrolyte abnormalities and volume overload.
3. Use of non-sterile isotonic fluid options may be ill-advised due to the potential for mixing errors, bacterial and endotoxin contamination, and increased risk for catheter site complications.
4. Normal saline has been repeatedly reported to result in hyperchloremic metabolic acidosis, which in other species has been associated with complications and possibly poorer outcomes. As such, balanced electrolyte solutions are likely preferable in the majority of patients. Exceptions include situations in which these effects may be therapeutic (i.e., in cases of hypochloremic metabolic alkalosis). There are more debatable benefits in cases of hyperkalemia.
5. While the proposed mechanism by which colloids exert their effects has been questioned, the equine literature to date does support their influence on colloid oncotic pressure and volume expansion.
6. Synthetic colloid administration has been shown to exert some, albeit mild, effects on hemostatic parameters similar to those seen in people and small animal patients, particularly at higher doses. As such, it may be wise to limit their administration to lower doses. It is important to note that there is no data from which to evaluate the potential for additional side effects seen in other species.

As can be seen throughout this review, with respect to evaluating fluids in the context of being a drug, the preponderance of the equine literature has focused on the first two "Ds" - drug and dosing - but very little has been evaluated with respect to duration or de-escalation. Work in other species has shifted to consideration of how these factors influence outcome, with particular emphasis on concerns such as fluid overload (68). This has resulted in a move toward consideration of fluid therapy not as a sole treatment modality with a prescribed drug, dose, and route, but rather a therapeutic intervention with 4 phases: the resuscitation phase, the optimization phase, the stabilization phase, and the evacuation phase (2, 68). Largely, to date, the average equine practitioner has likely considered the resuscitation and stabilization phases, but probably overlooked the later phases. However, some clinical research has recently been performed evaluating the possible implications of aggressive fluid therapy – such as the aforementioned study examining the effect of high IV fluid rates on intestinal hydration and another evaluating the relationship between IV fluid administration and development of post-operative reflux (36, 69). It is encouraging to see a move toward this type of thinking and greater consideration of the implications of failing to reflect on these repercussions for the patient.

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Effect of Feed Intake on Water Consumption in Horses: Relevance to Maintenance Fluid Therapy

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Maintenance fluid therapy is challenging in horses that cannot drink or are denied feed and water because of concerns about gastrointestinal tract function and patency. Intravenous fluid delivery to meet water needs based on current recommendations for maintenance requirements were obtained in fed horses and therefore might not apply to horses that are not being fed. This is a critical flaw because of the interdependence between intestinal tract water and extracellular water to support digestion while preserving water balance, a concept explained by the enterosystemic cycle. Because horses drink less when they are not eating and hence have lower water needs than fed horses, maintenance water requirements need to be adjusted accordingly. This article reviews this topic and identifies benefits of adjusting maintenance fluid therapy to meet lower demands from gastrointestinal function, such as reduced volumes, lower cost, avoidance of overhydration.

Keywords: horse, water consumption, feed intake, maintenance therapy, fluid therapy

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Water is an essential nutrient for all mammals (1), especially the horse, a large herbivore with considerable water needs to support microbial fermentation in its voluminous hindgut. Water is generally provided to horses in two forms, as maintenance and replacement solutions. The latter involves intravenous infusion of large volumes of physiologic solutions with water and electrolyte composition similar to plasma, and is usually given to replace losses through disease (fluid resuscitation). Such fluid therapy is challenging because reliable guidelines for safe and effective infusion rates and volumes are poorly developed in veterinary medicine (2).

MAINTENANCE RATES OF WATER INTAKE

Maintenance fluid intake refers largely to water required to offset water losses through insensible routes (skin and lungs) and through excretory processes (urine and feces) (3–5). In healthy, euvolemic horses with a functional gastrointestinal tract, this is satisfied through voluntary water consumption, which is also used as the method to determine maintenance water requirements. Provision of maintenance fluids to horses with a nonfunctional gastrointestinal tract is more challenging and is prone to error (see below).

The widely accepted maintenance requirement of water for horses is approximately 60 ml/kg/day (2 to 3 ml/kg/h), or approximately 30 L/day for an average adult nonbreeding, nonworking horse (500 kg body weight) (5–7). In addition to consumed water, water is also provided in the feed, which could contribute ∼3 ml/kg/day or ∼1.6 L/horse/day (8, 9). Added to this is unmeasured water from metabolic oxidation, ∼5 ml/kg/day (8, 9). When these

sources are included, horses consume 62.4 to 71.4 ml/kg/day (6, 8–11). Water excretion through feces can be 2.5 to almost 3 times mean urine volume (9), although the opposite relationship has also been recorded, explained by variations in ration composition and between study subjects (10). Insensible loss of water through skin and lungs could be estimated at 5.2 to 16.8 L/500 kg/day (9–11), with higher volumes in response to activity and high ambient temperatures (12–14). Visible sweating is not required to produce evaporative losses of water and electrolytes through skin (10).

Water needs increase with increased salt and protein intake, dietary effects (7), forage intake (15), transportation (16–18), athletic activities (12, 13), and fever (14). Lactating mares can increase water consumption by 37 to 74% above maintenance needs to meet milk production (19, 20). Foals, especially neonates, also handle water differently compared to adults, and this needs to be factored into their fluid therapy, and they are at risk of overhydration because of their small size (21). Healthy neonatal foals <24 h old have larger fluid compartments than adult horses and have an almost fetal system for fluid distribution that allows fluid movement from a large interstitial fluid space to preserve intravascular volume. Whereas, adults retain 20 to 50% of IV isotonic fluids in the intravascular space for 30 to 60 min after infusion, intravascular retention in the neonate is only 6 to 7% of the infused volume (21). This can be explained by the high capillary filtration coefficient that causes a rapid fluid movement into the interstitial fluid in response to a transient increase in capillary pressure (21). The fetal interstitium contains more ground substance and is quite compliant, so it can hold large amounts of fluid without generating increased interstitial pressure or edema (21).

Feeding schedules (22, 23) and dietary management (24) can profoundly influence maintenance water consumption in horses, which suggests that water intake is regulated to support feed consumption. More digestible hay-grain diets induce lower water consumption than hay only, which has been attributed to the lower needs for water to aid excretion of the smaller intestinal bulk (7). High dry matter content and cell wall constituents in the diet also increase water intake (7). Legume forages high in protein, such as alfalfa, require as much water as grass forages but induce a greater urinary excretion of water (7, 8). In horses transitioned from pasture to stall management with controlled exercise, water consumption doubled on all recorded days after the transition, total fecal output decreased by about half, and fecal dry matter content increased compared with pasture measurements (24). These changes in intestinal water, along with decreased motility in different parts of the large colon (on ultrasound examination), could be implicated as possible causes of colonic impactions (24).

EFFECT OF FEED INTAKE ON WATER CONSUMPTION

Maintenance fluid requirements have been determined on fed horses, and so might not be clinically relevant to horses denied feed, are unable to eat, or are unwilling to eat as part of their response to their primary disease and its treatment. Other examples are healthy euvolemic horses deprived of feed for sporting activities (17), transport (12, 16), and general anesthesia (25), or are anorexic or denied feed for any reason (6, 26–28). Maintenance water needs in horses can be influenced by feed intake, largely through the role of water in the extracellular fluid (ECF) space to support digestive processes in the intestinal lumen (22) (enterosystemic cycle; see below). Because 30–55% of daily water loss is accounted for in feces, horses off feed defecate less and require less water than fed horses with normal fecal output (6).

The effects of feed deprivation vs. feeding on voluntary water consumption was studied in eight healthy adult Thoroughbred geldings in a randomized crossover design, with each horse serving as its own control (fed conditions) (11). Feed deprivation reduced water consumption to ∼16% of fed values immediately after feed was denied, and this persisted with evidence of mild dehydration only on day 4 (11). When unmeasured variables are considered, such as water from feed and metabolic water (9), the difference in total water intake between feed deprivation (10.3 ml/kg/day) and the fed state (71.4 ml/kg/day) was even greater than indicated by voluntary water consumption only (11).

Water consumption in ponies denied feed in another study decreased to 27% the volume consumed when they were fed (29). Because water turnover is directly related to metabolic weight (30), water needs established for ponies are probably unsuitable for large-breed horses (10). The diarrhea that developed in three of eight horses toward the end of a 4-day interval without feed (11) is difficult to explain and could possibly be attributed to altered microbiota (31) and VFA production (32) or by alteration of the enterosystemic cycle when digestive processes are interrupted.

ENTEROSYSTEMIC CYCLE

The relationship between consumed water, the intestinal tract, and the horse's hydration status are demonstrated in the enterosystemic cycle (**Figure 1**). The enterosystemic cycle describes how ECF water is used to support enzymatic and microbial digestion and is then reclaimed during the interdigestive period to preserve the ECF volume (22, 33) (**Figure 1**). This water movement is characterized by periods of net influx and efflux, driven by a cyclic pattern of microbial digestion in response to feed intake (33). This relationship between the ECF and gut also plays a critical role in survival in an arid environment by preserving systemic hydration through water absorption from a hindgut reservoir that seems anatomically and physiologically well-suited for that purpose (4, 5, 8, 34).

Horses drink predominantly in the early postprandial period (11, 35), presumably to correct dehydration induced by influx of extracellular water into the gastrointestinal tract (22) in response to the meal-induced increases in osmotic load (3) and to support enzymatic and microbial digestion (33). This high volume of water influx into the intestine in response to digestion can induce a 15% reduction in plasma volume, sufficient to activate

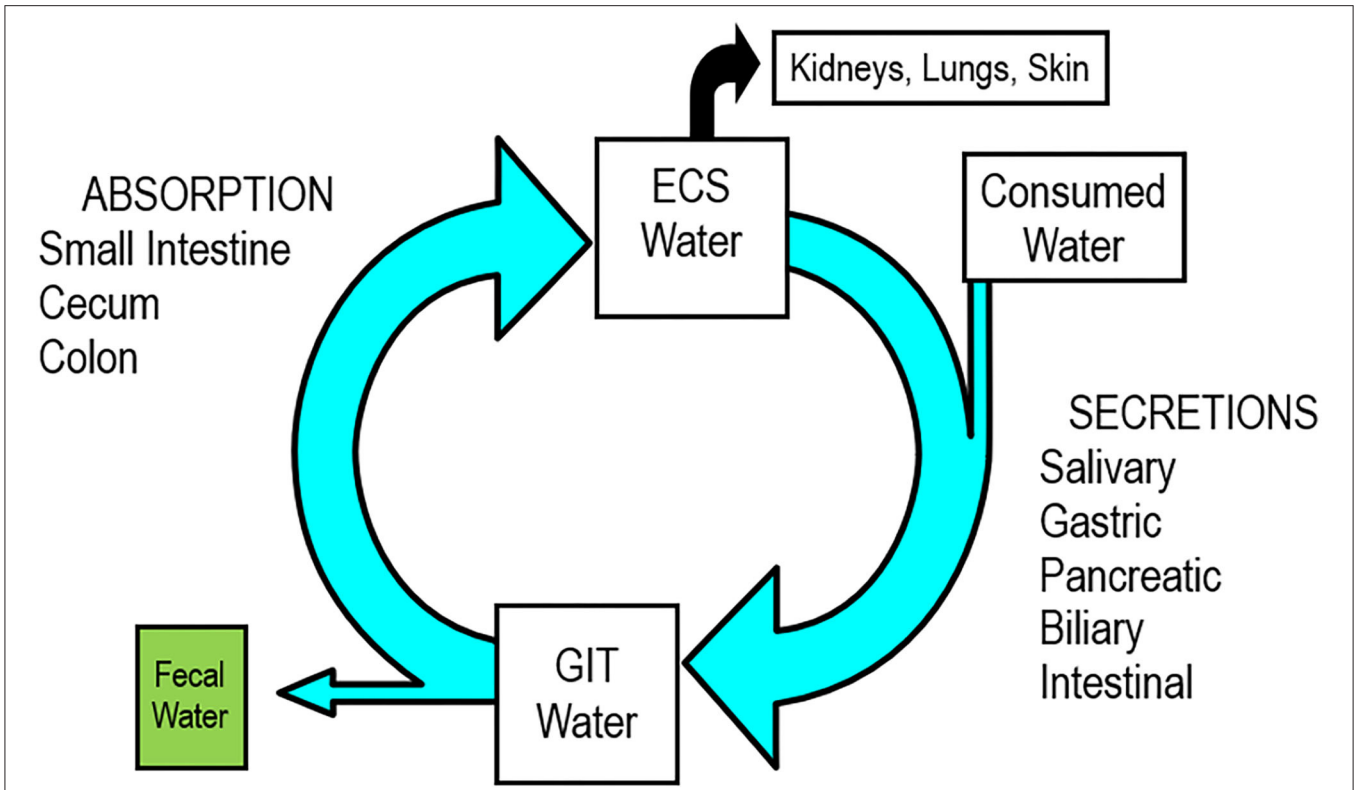

FIGURE 1 | Enterosystemic cycle in the healthy horse, to demonstrate the interplay between the gastrointestinal tract and the extracellular fluid (ECF) space. Absolute values are not included, which would identify the relative contributions of each process or segment to the overall scheme, although different sizes of arrows and boxes represent approximate relationships. Font sizes do not represent differences, such that the cecum and colon are responsible for greater water and electrolyte absorption than the small intestine.

the renin–angiotensin–aldosterone system. This response could contribute to water reabsorption (22) (**Figure 1**). Aldosterone can double Na^+ and presumably water reabsorption by the ventral and dorsal colons and can triple these responses in the small colon (36).

Most of the water horses consume quickly reaches the large intestine, either through rapid and direct transit (33) or through small intestinal absorption followed by colonic secretion (8). This consumed water contributes to a substantial reservoir of water and electrolytes in the gastrointestinal tract, with 74% to 81% in the large intestine, and the remainder in the stomach and small intestine (37). Water constitutes more than 80% of intestinal contents (37), which means that a horse with a digestive tract capacity of 120 to 150 L has a water reservoir of >100 L in the intestinal tract (5). Because colon contents account for 13% body weight (38), as much as 50 L of water per 500-kg body weight can be contained in this segment (4, 9). Daily water reclamation from the colon to preserve the ECF requires reabsorption of the equivalent of >95% of the Na^+, HCO_3^-, and water in the animal's ECF volume (33).

The enterosystemic cycle presumably undergoes lower rates of water exchange in horses managed by high-frequency meal feeding programs that are more natural than the typical twice a day feeding of hay and grain (22). Possibly, the natural grazing system preserves the ECF water more efficiently, which could explain why feral horses can travel up to 55 km from water and thereby tolerate large intervals between watering (39). The lack of feed from overgrazing close to the water source (39) could reduce feed intake in the feral horse as its water needs increase, thereby reducing demand on ECF water to support digestive processes when water is scarce.

THE ROLE OF THIRST

Water consumption is driven by internal cues prompted by dehydration and hypovolemia (40) and combines with water absorbed from the colon (4) if needed as an auxiliary source. Many osmotic, ionic, hormonal, and neural signals are integrated within the central nervous system to stimulate water consumption (40). Water consumption is positively correlated with plasma osmolality in horses (3, 8, 40, 41), which is accounted for mostly by plasma Na^+ (8). Plasma Na^+ can decrease in horses during feed deprivation (11), probably from reduced intake and increased urinary loss (5). Feed deprivation, with (5, 26) or without water deprivation (11), can induce diarrhea in horses, which could also increase fecal loss of Na^+ (42). Horses allowed to eat hay but denied water will develop a free water deficit,

with increased serum Na^+ concentration, serum osmolality, and thirst (8).

The response to thirst in horses can rapidly correct dehydration from water deprivation or water loss and effectively restore plasma osmotic pressure and blood volume (3). A 3% increase in osmolality or 8 mOsm increase will stimulate thirst, which is similar to other animals (3). Even minor cellular dehydration is a powerful stimulus to osmoreceptive neurons in the preoptic/hypothalamic region of the brain (40) and would be expected to stimulate thirst in horses (43). Horses will drink in response to an isosmotic loss of blood volume of 6% (3), which is considerably less than the 15% loss in plasma volume recorded in horses within 1 h after they start a large meal. This could explain the role of voluntary postprandial drinking to restoring early water loss during meal feeding. However, "involuntary dehydration" has been reported in endurance horses, possibly by an unknown mechanism that could dampen the thirst drive (12). Ponies that are deprived of water can also overcompensate by drinking more than would be expected, presumably to restore the water reservoir in the colon (3). During initial rehydration after a period of water deprivation, most of the consumed water in equids accumulates in the hindgut (4), either through direct passage or small intestinal absorption followed by secretion into the hindgut (8).

Peripheral or visceral osmoreceptors can also modify water consumption (44). Visceral osmoreceptors are located in the upper parts of the alimentary tract, oropharyngeal cavity, gastrointestinal tract, and liver (44). These detect consumed dilute fluids and preemptively signal the inhibition of vasopressin release (44).

REPLACEMENT FLUID THERAPY

Fluid therapy in horses is typically designed to correct fluid deficits from diarrhea, gastrointestinal reflux, or prolonged sweating or to support altered hemodynamic status with maldistributive shock. It is guided in veterinary medicine by crude clinical and laboratory indicators of efficacy (2). Such therapy also provides for maintenance needs (45), and in fact, resuscitative strategies for horses with postoperative reflux, a well-known source of copious fluid loss, typically include maintenance delivery rates as the standard approach in most hospitals (46, 47). Because these horses are not eating, they are actually receiving multiples of maintenance delivery rates, based on the 16% reduced water needs compared with fed values. This approach is probably of little consequence if it offsets fluid losses as intended, especially in these horses that are so dependent on fluid therapy to offset intestinal losses and to preserve renal function. However, a more conservative approach guided by meaningful measures of fluid responsiveness would probably benefit many of these cases and avoid any risk of overhydration (48–51). A heavy reliance on traditional maintenance rates in horses without a measure of fluid responsiveness could lead to overhydration, especially during anesthesia, when horses with colic can receive up to 15–25 ml/kg/h, with a mean of 19.5 ml/kg/h in one study (48).

Awareness of problems with overly aggressive fluid therapy in human patients and small animals and current concepts about fluid responsiveness (2, 49–51) could be relevant to horses. Excessive administration of Na^+-rich crystalloids could be potentially harmful in human patients (49) and could reduce colloid osmotic pressure to levels associated with decreased survival in horses (52). A low intraoperative PCV in horses could predict failure to recover from anesthesia and the need for postoperative gastric decompression (53), possibly as an adverse response to overhydration. Although horses have developed efficient homeostatic mechanisms for dealing with hypovolemia, a consequence of evolving to survive in arid environments (4, 34), they might not be equipped to manage a largely iatrogenic and unnatural phenomenon such as volume overload (51).

Volume overload can release natriuretic peptides from myocytes in response to increased cardiac filling pressures, and these peptides cleave membrane-bound proteoglycans and glycoproteins from the endothelial glycocalyx (EGL) (51, 54). This complication is exacerbated by existing endothelial damage in patients with sepsis, leading to a rapid shift of intravascular fluid into the interstitial space with tissue edema (51) and impaired lymphatic drainage (54).

The intestine seems to be more prone to edema formation than the lungs and skeletal muscle (55), possibly because of its relatively large extracellular space compartment (56). In a murine model of postoperative ileus (POI), high volume resuscitation and mesenteric venous hypertension caused significant intestinal edema and decreased small intestinal transit (57). Intestinal edema alone can initiate or propagate dysfunctional signaling pathways that disrupt intestinal contractility, even in the absence of neutrophil inflammation and mucosal injury (57, 58). This problem could be self-perpetuating, because lymph flow from intestine depends on peristalsis, so reduced lymphatic outflow in hypomotile intestine could exacerbate the intestinal edema (57, 58). Increased capillary permeability from shock and ischemia/reperfusion injury could also contribute to fluid leakage into the interstitium (57) and further impair gastrointestinal function following crystalloid infusions. Intestinal wall edema can also cause translocation of endotoxin or bacteria (50), increase intraabdominal hypertension (IAH), and even cause abdominal compartment syndrome (59).

MAINTENANCE FLUID THERAPY

When the need for replacement fluid therapy has ended in the hospitalized horse, and it is considered no longer in shock or dehydrated, but is not being fed, then maintenance fluid at conservative rates can be given. Typical examples are horses with medically responsive colic, horses that have restricted access to feed and water for any reason, and horses with botulism or other causes of dysphagia, resolving colitis, or because recovery of alimentary tract function is incomplete (6) (oral, pharyngeal, esophageal injury, or gastrointestinal disease). Although voluntary water consumption would be ideal in such cases, concerns about function of the alimentary tract could necessitate IV infusions.

Maintenance fluids for IV administration, such as the commercially available "half strength" saline with dextrose (0.45% NaCl and 2.5% or 5% dextrose in water), can provide free water through dextrose metabolism (6). Dextrose-containing solutions could also be of benefit to miniature horses, ponies, and donkeys, because these are prone to hyperlipidemia, and to pregnant and lactating mares, because of their considerable energy needs (20). Some maintenance solutions lack K^+, other electrolytes, and alkalinizing agents, and others provide a higher concentration of K^+ than replacement fluids (6). The equal concentrations of Na^+ and Cl^- (77 mEq/L) in these fluids produce a strong ion difference (SID) of 0, which could lead to hyperchloremic metabolic acidosis if given in high volumes (54). Hyponatremia is a possible but unreported complication with hypotonic maintenance fluids in horses (6). Although clinical and laboratory assessment of response to fluid therapy should be applied to horses on maintenance fluids, maintenance of a normal central venous pressure (CVP) could also be considered a reasonable goal to prevent edema, with high normal CVP regarded as the acceptable upper limit (6). However, this is a technically difficult measurement and of questionable value for measuring intravascular volume (51).

The critical problem with current maintenance fluid therapy is that the appropriate fluids are not available in the volumes perceived as necessary to meet maintenance needs of horses (60), and consequently, commercial replacement/resuscitation fluids in 5-L bags are used instead. However, these fluids are designed to replace water and electrolyte losses on an equivalent basis to plasma and are therefore too rich in Na^+ for maintenance needs (8, 14, 60). In horses, an all-hay diet without salt supplement would provide 329 to 440 mEq of Na^+ daily (9), less than the Na^+ contained in 3 L of a commercially available balanced electrolyte solution (133 to 140 mEq/L). Therefore, a horse supplemented with a replacement electrolyte solution infused at the currently proposed maintenance rate (60 ml/kg/day) would receive almost 10 times its normal daily intake of Na^+. Such Na^+-rich fluids can induce sufficient diuresis to increase urinary losses of K^+, Ca^{++} and Mg^{++} (8, 60–62). A balanced electrolyte solution infused IV at one to three times the current maintenance rate can cause net secretion of Na^+ into the intestinal tract, quadruple fecal Na^+ output, and decrease serum Na^+ concentration in water-deprived horses (8). The Na^+ influx into the gastrointestinal tract would entrain an influx of water with it to preserve osmotic equilibrium, and such water movement could cause dehydration (8, 14).

The preceding concerns can be resolved by infusing maintenance-purpose fluids in rates more appropriate for horses on feed restriction, which is about 16% of the current maintenance rates determined for fed horses (11) (∼10 ml/kg/day). Such rates of infusion would also reduce the difficulties with currently available maintenance fluids, such as availability in small volumes, excessive dextrose infusion, high cost, and possibilities of hyponatremia and overhydration. However, further studies are required to demonstrate such benefits.

CONCLUSIONS

Fluids constitute one of the single most expensive components of the total cost of colic treatment in a hospital setting, for both medical and surgical cases (63), and their use should be guided by an understanding of the many variables that underlie water balance in the horse. Recent research findings should increase awareness in horse owners and veterinarians that water consumption in equids can be considerably altered by feed consumption (11). Further research is needed to explore the many variables relevant to rehydration of sick horses and maintenance needs under different clinical conditions.

AUTHOR CONTRIBUTIONS

DF is the sole author, responsible for all parts of manuscript generation.

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Comparative Trial of Continuous Flow Enteral and Intravenous Fluid Therapy in Horses

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Continuous flow enteral fluid therapy with isotonic and hypotonic enteral electrolyte solutions are as safe and effective as intravenous fluid therapy. The aim of this study was to carry out a comparative assessment between continuous flow enteral and intravenous (IV) fluid therapy in adult experimentally dehydrated horses. Six experimentally dehydrated adult mares were used in a study carried out in a 6 × 3 crossover design, which each animal received three different treatments (isotonic enteral fluid therapy—EsISO, hypotonic enteral fluid therapy—EsHYPO and intravenous fluid therapy with Lactate Ringer Solution—LR IV, all in continuous flow). Solutions were administered at a rate of 15 $mL^{-1}.kg^{-1}.h^{-1}$ for 8 h, after 36 h of water and food deprivation. Serum and urinary biochemical assessment; urinary volume, pH and specific gravity; and blood gas analysis were measured at −36, 0, 2, 4, 6, and 8 h. The dehydration period (DP) caused discrete hydroelectrolytic and acid base imbalances. The EsISO, EsHYPO and LR IV increased blood volume. Enteral solutions restored the imbalances yielded by the DP and all treatments increased urine volume. Also, the EsHYPO and LR IV showed no effects in acid base balance, while EsISO showed slightly acidifying effect. The present study certifies the efficacy and safety of isotonic and hypotonic continuous flow enteral fluid therapy in comparison to IV fluid therapy in dehydrated horses.

Keywords: equine, dehydration, rehydration, enteral fluid therapy, intravenous fluid therapy, isotonic, hypotonic

INTRODUCTION

The therapeutic choice to regulate water, electrolyte and acid-base imbalances in horses is fluid therapy. Solutions containing electrolytes and other elements (such as energy sources) are administered to restore blood volume and perfusion in addition to rehydrate tissues and digesta. Among the different modalities of hydroelectrolytic therapies, the intravenous (IV) administration of commercial electrolyte solutions is traditionally considered the most effective (1) and also the most employed in equine medicine.

The administration of electrolytic solutions through the nasogastric route is also routinely used in horses, but to a lesser extent when compared to the intravenous modality. Enteral fluid therapy (EFT) via the nasogastric route has been studied with excellent results in the equine species (2–4). In EFT electrolyte solutions are infused directly into the gastrointestinal tract in order to be absorbed towards the plasma compartment.

In cases that are not severely dehydrated or at risk of hypovolemic or endotoxic shock, EFT has been shown to be as efficient as IV fluid therapy. In addition to being easily applicable, it allows modifications in the composition of electrolyte solutions in order to satisfy the needs of each patient, improving the efficacy of the solutions and enhancing the success rate of this therapy (5).

In recent years, EFT started to be administered by continuous flow (EFTcf). In this modality, electrolyte solutions are administered continuously for prolonged periods through small gauge nasogastric or nasoesophageal tubes. Thus, daily infusion of large volumes of solutions is possible without triggering any kind of discomfort—neither by the presence of the tube itself, nor due to abdominal distention. This has been proved true in the authors' clinical experience after years using EFTcf. Despite all that, this fluid therapy method is not widespread, remaining as a therapeutic modality restricted to Veterinary Hospitals.

To date, only one study (6) has been conducted comparing the use of intravenous Ringer's lactate solution with EFT. The aim of this study was to compare continuous flow enteral fluid therapy and IV fluid therapy in experimentally dehydrated adult horses. Our hypothesis was that EFTcf with isotonic and hypotonic electrolyte solutions is as effective as IV fluid therapy in rehydrating horses.

MATERIALS AND METHODS

Six non-pregnant Warmblood mares, with an average age of 10 ± 3 years and median body weight of 436 ± 40 kg, were used in the present study. All horses were considered healthy based on clinical and laboratory tests. Animals were housed in individual stalls, fed Tifton grass hay (Cynodon sp.), commercial concentrate (1 to 2% of body weight divided into 3 meals) and allowed free access to water and mineral supplement *ad libitum*. The experimental design was a 6 × 3 crossover. Each mare received all three treatments, one at a time in a rotational system with a washout period of 8 days. The mares were experimentally dehydrated prior to the fluid therapy phase. The dehydrating period (DP) consisted of 36 h of food and water deprivation associated with the administration of two doses of furosemide (1 mg kg^{-1}, 12 h apart, IV). After the DP the animals received a hypotonic (EsHYPO) or an isotonic enteral electrolyte solution (EsISO) through a nasogastric tube (5 mm of internal diameter x 7 mm of external diameter and 1.5 m in length) or lactated Ringer's solution (LR IV) intravenously through the jugular vein with a 14-gauge catheter, all in continuous flow at a rate of 15 ml kg^{-1} h^{-1} for 8 h (fluid therapy period). The presence of the nasogastric tube in the stomach was confirmed by the return of gastric contents after aspiration.

TABLE 1 | Composition of enteral and intravenous electrolyte solutions.

Components	EsHYPO	EsISO	LR IV
Sodium chloride	4 g	5 g	6 g
Potassium chloride	0.5 g	0.5 g	300 mg
Calcium acetate	1 g	1 g	---
Calcium chloride	---	---	200 mg
Magnesium chloride	0.2 g	0.2 g	---
Sodium lactate	---	---	3.1 g
Dextrose	---	10 g	---
Maltodextrin	5 g	---	---
Osmolarity	190 mOsm L^{-1}	280 mOsm L^{-1}	274.1 mOsm L^{-1}

EsHYPO, hypotonic enteral electrolyte solution; EsISO, isotonic enteral electrolyte solution; LR IV, intravenous lactated Ringer's solution (Fresenius Kabi Brasil Ltda. – Barueri – SP).

The concentrations of each electrolyte solution used are described (**Table 1**).

Blood samples were collected immediately before the start of the dehydration protocol (T-36 h, baseline values), at the end of the DP (immediately before the start of treatments) (T0h), two (T2h), four (T4h), six (T6h), and 8 h (T8h) after the beginning of treatments. Blood was collected for biochemical tests by jugular venipuncture using Vacutainer BD vials (Curitiba - PR - Brasil). To obtain serum, blood samples were collected in Vacutainer BD® tubes without anticoagulant and with clot activator and kept in a water bath at 37°C for 40 min, for clot formation. Serum separation was performed by centrifugation and then stored at −20°C until analysis. Chloride, magnesium, phosphorus, urea and creatinine concentrations were determined in serum samples by colorimetric enzymatic assay in the automatic biochemistry device Bioplus Bio 2000 (Laboratory Products Bioplus, Barueri-SP). Plasma glucose and lactate were determined on the same device. Serum osmolarity was determined by freezing point depression (Osmometer 3320, Advanced Instruments Inc, Massachusetts, USA).

Sodium, potassium, ionized calcium, and blood gas parameters (pH, pCO_2, HCO_3^- and Base Excess) were evaluated on i-STAT Handheld Blood Analyzer (Abbot Point of Care Inc, Princeton, USA), by collecting 2 ml of blood from the jugular vein with a BD® needle and heparinized syringe immediately after the blood sample collection. Anion Gap (AG) was calculated using the equation: $AG = (Na^+ + K^+)–(Cl^- + HCO_3^-)$, while the strong ions difference (SID) was based on the formula $SID = [(Na^+ + K^+)–(Cl^-)]$ (7).

Urine volume was measured at every experimental time from T0h to T8h through a graduated collection bag connected to a 24-gauge Foley Rusch (3). Urine aliquots were collected to determine specific gravity through refractometry (Refractometer—Model 8494) and pH and glucose on a reagent strip (Combur Test—Roche). Urinary chloride, calcium, magnesium, urea and creatinine were measured by biochemical analysis (HumaStar 300 Automated Chemistry Analyzer, Human Diagnostics,

Wiesbaden, Germany), while urinary sodium and potassium were determined by flame photometry (Photometer B462, Micronal, São Paulo, Brazil).

Results were analyzed using the statistical program SPSS 13.0. Quantitative variables were subjected to the Normality (Shapiro-wilk) and Homoscedasticity (Cochran) tests to verify if ANOVA requirements were met. If so, an analysis of variance based on planning of repeated measures was used to assess the effect of treatments, that is, each treatment at different times. The influence of time and the interaction between treatment and time were also analyzed. When the analysis showed a significant effect for one or more factors, Tukey test was applied to compare any and all contrasts between two treatment averages. All analyses were interpreted considering a significance level of 5%. When normality criteria were not met, differences between treatments in the same period were assessed using the Kruskal—Wallis test and differences within a treatment at different times using the Friedman test.

RESULTS

The DP did not affect serum sodium levels. During the fluid therapy phase, significantly higher sodium levels were observed in the LR IV treatment group (T2h, T4h, and T6h) in comparison to EsISO and EsHYPO (**Table 2**).

The DP caused a significant decrease in serum potassium, chloride and ionized calcium in comparison to baseline values (T-36h). Serum potassium returned to baseline during the fluid therapy phase in all three treatment groups at T6h and T8h (**Table 2**). Serum chloride returned to baseline in the EsHYPO and RL IV group and values above baseline were observed in the EsISO group at T4h, T6h, and T8h. Ionized calcium returned to baseline in the EsHYPO and EsISO treatment groups but remained lower than baseline in the LR IV treatment group (**Table 2**).

A significant increase in serum magnesium, phosphorus, urea, creatinine, lactate, glucose, and osmolality in comparison to baseline values (T-36h) was noted after the DP (**Tables 2**, **3**). During the fluid therapy phase magnesium decreased even further in all three groups and more profoundly in the LR IV treatment at T8h. Phosphorus returned to baseline in the EsISO and EsHYPO treatment groups but remained higher than baseline in the RL IV group. Glucose levels were significantly higher than baseline during the first hours of EsISO and EsHYPO treatments, returning to baseline at T8h on both groups. Glucose levels remained in the reference range during the entire fluid therapy phase in the LR IV treatment group (**Table 3**). All three treatments were effective in correcting urea, creatinine, lactate and osmolarity values back to baseline (**Tables 2**, **3**).

A significant increase in urinary sodium, potassium, magnesium, creatinine and urea in comparison to baseline values (T-36h) was noted after the DP (**Tables 4**, **5**). Urinary sodium decreased in the EsHYPO and EsISO groups and increased in the LR IV group during the fluid therapy phase (T4h, T6h, and T8h). The DP caused a significant decrease in urinary chloride and calcium. Urinary chloride remained low throughout the fluid therapy phase in the EsISO and EsHYPO treatment groups, while a gradual increase was noted in the LR IV treatment starting at T6h (**Table 4**). Urinary potassium also decreased in all three groups during the fluid therapy phase (**Table 4**). Urinary calcium remained lower than baseline during the fluid therapy phase in all three treatment groups (**Table 4**). Urinary magnesium returned to baseline values at T8h in the EsISO and EsHYPO treatment groups and values below baseline were noted in the LR IV treatment group at T8h (**Table 4**). Urinary urea and creatinine decreased over the hydration phase in all three treatment groups (**Table 5**).

Groups treated with enteral electrolyte solutions, which had the addition of energy sources, demonstrated an increase in urinary glucose after T2h, with EsISO treatment animals showing the highest values (**Table 5**).

During the fluid therapy phase all treatments caused a gradually increase in urine volume from T4h to T8h, with the highest volume observed in the LR IV treatment group at T8h. The DP did not affect urinary pH. Significantly higher pH values in comparison to baseline (T-36h) were observed only in the LR IV group at T4h and T6h. The urine specific gravity suffered a significant increase in comparison to baseline (T-36h). All treatments returned urine specific gravity values to baseline values (**Table 6**).

A significant effect of the DP on acid base balance was noted and characterized by an increase in pH, HCO_3^- and BE. Likewise, SID values increased after DP. The three treatments caused a decrease in pH, HCO_3^-, BE and SID, while pCO_2 and AG values throughout the experimental phase showed little variation in all treatment groups (**Table 7**).

DISCUSSION

Serum sodium was not affected by the experimental dehydration protocol and during the fluid therapy phase in the EsHYPO and EsISO groups (**Table 2**). Therefore, the hypotonic enteral solution used in the present study is safe to rehydrate horses without causing hyponatremia, which is the major concern with this type of fluid. The DP caused an increase in urinary sodium (T0h) in comparison to baseline (T-36h), but during the fluid therapy phase values returned to baseline in the EsHYPO and EsISO treatments at T4h (**Table 4**). This was possibly a result of the composition of the electrolyte solutions associated with an increase in urinary output due to fluid therapy and urine dilution and decreased urinary sodium excretion. Similar results have been reported in adult horses (5). However, weaned foals treated with enteral electrolyte solutions for 12 h at the same infusion rate used in the present study showed an increase in urinary sodium excretion (4).

Serum sodium levels did not significantly change within the LR IV group during the fluid therapy phase but were significantly higher than those observed in the EsISO and EsHYPO treatments at T2h, T4h, and T6h (**Table 2**). This can be attributed to the composition of lactate Ringer's solution (LRS), which contains more sodium than the enteral electrolyte solutions used in the present assay. This effect was transient and lacks clinical

TABLE 2 | Means and standard deviations of serum sodium (mmol L^{-1}), potassium (mmol L^{-1}), chloride (mmol L^{-1}), ionized calcium (mmol L^{-1}), magnesium (mg dl^{-1}), and phosphorus (mg dl^{-1}) in horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities.

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Serum sodium						
EsHYPO	$134.00^{Aa} \pm 2.53$	$133.17^{Aa} \pm 5.53$	$130.17^{Aa} \pm 5.34$	$130.00^{Aa} \pm 4.47$	$131.33^{Aa} \pm 4.37$	$134.00^{Aa} \pm 4.56$
EsISO	$134.17^{Aa} \pm 4.88$	$133.67^{Aa} \pm 3.33$	$131.00^{Aa} \pm 2.53$	$130.67^{Aa} \pm 1.75$	$132.50^{Aa} \pm 1.87$	$134.50^{Aa} \pm 3.27$
LR IV	$133.17^{Ba} \pm 5.56$	$134.17^{Ba} \pm 4.83$	$134.67^{Aa} \pm 4.72$	$134.83^{Aa} \pm 4.58$	$135.17^{Aa} \pm 4.22$	$134.67^{Ba} \pm 4.50$
Serum potassium						
EsHYPO	$4.30^{Aa} \pm 0.37$	$3.38^{Ab} \pm 0.31$	$3.55^{Ab} \pm 0.29$	$3.75^{Ab} \pm 0.26$	$3.85^{Aa} \pm 0.19$	$3.93^{Aa} \pm 0.15$
EsISO	$4.13^{Aa} \pm 0.85$	$3.50^{Ab} \pm 0.32$	$3.53^{Ab} \pm 0.28$	$3.57^{Ab} \pm 0.22$	$3.73^{Ba} \pm 0.23$	$3.85^{Aa} \pm 0.15$
LR IV	$3.90^{Aa} \pm 0.35$	$3.47^{Ab} \pm 0.34$	$3.50^{Ab} \pm 0.33$	$3.48^{Ab} \pm 0.25$	$3.55^{Ba} \pm 0.19$	$3.65^{Aa} \pm 0.25$
Serum chloride						
EsHYPO	$98.50^{Ab} \pm 4.32$	$94.83^{Ac} \pm 3.66$	$96.83^{Ac} \pm 3.19$	$97.17^{Ab} \pm 3.13$	$104.00^{Aa} \pm 3.58$	$101.17^{Bb} \pm 4.31$
EsISO	$101.00^{Ab} \pm 3.69$	$95.83^{Ac} \pm 5.74$	$98.67^{Ac} \pm 2.42$	$100.33^{Ab} \pm 3.20$	$102.00^{Aa} \pm 2.37$	$105.50^{Aa} \pm 3.27$
LR IV	$99.50^{Aa} \pm 2.43$	$94.33^{Ab} \pm 1.75$	$97.50^{Ab} \pm 3.08$	$98.33^{Aa} \pm 1.75$	$98.17^{Ba} \pm 2.56$	$100.83^{Ba} \pm 2.56$
Serum ionized calcium						
EsHYPO	$1.75^{Aa} \pm 0.07$	$1.56^{Ab} \pm 0.16$	$1.84^{Aa} \pm 0.08$	$1.86^{Aa} \pm 0.18$	$1.81^{Aa} \pm 0.12$	$1.78^{Aa} \pm 0.12$
EsISO	$1.67^{Aa} \pm 0.08$	$1.51^{Ab} \pm 0.13$	$1.80^{Aa} \pm 0.14$	$1.85^{Aa} \pm 0.14$	$1.81^{Aa} \pm 0.13$	$1.80^{Aa} \pm 0.11$
LR IV	$1.73^{Aa} \pm 0.08$	$1.47^{Ab} \pm 0.15$	$1.47^{Bb} \pm 0.13$	$1.50^{Bb} \pm 0.15$	$1.50^{Bb} \pm 0.14$	$1.52^{Bb} \pm 0.16$
Serum magnesium						
EsHYPO	$1.68^{Ab} \pm 0.19$	$2.13^{Aa} \pm 0.23$	$1.65^{Bb} \pm 0.32$	$1.47^{Ac} \pm 0.19$	$1.38^{Ac} \pm 0.12$	$1.28^{Ad} \pm 0.08$
EsISO	$1.85^{Ab} \pm 0.36$	$2.25^{Aa} \pm 0.22$	$1.95^{Ab} \pm 0.28$	$1.58^{Ac} \pm 0.29$	$1.45^{Ac} \pm 0.24$	$1.40^{Ac} \pm 0.43$
LR IV	$1.65^{Ab} \pm 0.14$	$1.98^{Aa} \pm 0.15$	$1.20^{Cc} \pm 0.14$	$1.03^{Bd} \pm 0.14$	$1.03^{Bd} \pm 0.20$	$0.85^{Be} \pm 0.10$
Serum phosphorus						
EsHYPO	$1.87^{Ab} \pm 0.74$	$2.88^{Aa} \pm 0.84$	$2.57^{Aa} \pm 1.03$	$2.37^{Aa} \pm 0.92$	$2.27^{Ba} \pm 0.73$	$2.05^{Bb} \pm 0.41$
EsISO	$1.77^{Ab} \pm 0.60$	$2.98^{Aa} \pm 0.73$	$1.88^{Ab} \pm 0.69$	$1.65^{Ab} \pm 0.52$	$1.57^{Cb} \pm 0.58$	$1.47^{Cb} \pm 0.56$
LR IV	$1.92^{Ab} \pm 0.57$	$3.32^{Aa} \pm 0.51$	$2.90^{Aa} \pm 1.09$	$2.50^{Ac} \pm 0.69$	$2.55^{Ac} \pm 0.51$	$2.57^{Ac} \pm 0.81$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < 0.05$).

relevance, since sodium concentrations in the LR IV group did not exceed the normal range for horses (8). In addition, urinary sodium increased significantly ($P < 0.05$) during the fluid therapy phase in RL IV groups, indicating that the amount of sodium in the lactate Ringer's solution, despite being physiological, is high (**Table 4**). Similar results were observed in neonatal foals (9).

Serum potassium decreased following the DP ($P < 0.05$). Since forages are important sources of potassium (10), food restriction might have contributed to this finding. Also, furosemide increases renal excretion of potassium (11). During the fluid therapy phase from T6h on, all treatments were effective in bringing potassium levels back to baseline (**Table 2**), likely due to the presence of this electrolyte in all three fluids. An increase in urinary potassium was also observed after the DP, mainly due to the action of furosemide (**Table 4**). A gradual decrease was observed during the fluid therapy phase and values significantly lower than baseline were noted at T8h. As mentioned by Harrison-Bernard (12), the decrease in urinary potassium excretion may be associated with the plasma volume expansion caused by fluid therapy, reducing renal potassium excretion.

Serum chloride values decreased significantly during the DP (T0h), which is expected due to the action of furosemide (11). This phenomenon was not observed in another experiment where the dehydration induction protocol consisted of only 24 h of water and food deprivation combined with only one dose of furosemide 3 mg kg^{-1} of furosemide (13). All three fluids were able to reverse serum chloride depletion during the fluid therapy phase (**Table 2**), with the EsISO enteral treatment showing values above baseline at the end of the trial but still within the normal range (8). Despite containing more chloride than the enteral solutions, LR IV treatment did not promote an increase in serum values of this electrolyte. This can be justified by the fact that LR contains a similar amount of chloride as equine serum or plasma (105 mmol L^{-1}). Also, the RL IV group showed greater urinary chloride excretion, sustaining its serum levels unchanged. In order to maintain serum chloride levels, a lower urinary chloride excretion was noted in the EsHYPO and EsISO treatment groups (**Table 4**).

Serum ionized calcium decreased after the DP, mainly because of fasting and the diuretic action of furosemide, since horses' urine is rich in calcium (14). Both enteral therapies (EsISO and EsHYPO) were more efficient in maintaining serum levels of this element (**Table 2**). Serum ionized calcium remained below baseline at the end of the experimental period (T8h). Urinary Ca^{++} excretion also decreased in the DP and remained low during the hydration phase in the RL IV group (**Table 4**). This can be justified by the fact that lactated Ringer's solution (LRS) contains lower calcium levels than equine plasma (1). Also, it

TABLE 3 | Means and standard deviations of serum urea (mg dl^{-1}), plasma lactate (mmol L^{-1}), serum creatinine (mg dl^{-1}), plasma glocose (mg dl^{-1}), and serum osmolarity (mOsm L^{-1}) in horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities.

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Serum urea						
EsHYPO	$25.83^{Ab} \pm 9.77$	$51.33^{Aa} \pm 9.22$	$51.17^{Aa} \pm 10.25$	$47.67^{Aa} \pm 8.09$	$43.67^{Aa} \pm 7.74$	$38.50^{Ab} \pm 5.96$
EsISO	$25.83^{Ab} \pm 3.31$	$49.33^{Aa} \pm 5.57$	$50.33^{Aa} \pm 7.45$	$45.33^{Aa} \pm 7.26$	$38.67^{Aa} \pm 6.92$	$35.33^{Ab} \pm 4.68$
LR IV	$25.67^{Ab} \pm 9.05$	$52.00^{Aa} \pm 14.09$	$50.67^{Aa} \pm 9.11$	$50.50^{Aa} \pm 11.61$	$44.33^{Aa} \pm 7.28$	$38.00^{Ab} \pm 11.10$
Plasma lactate						
EsHYPO	$2.18^{Ab} \pm 0.88$	$4.13^{Aa} \pm 1.89$	$3.23^{Aa} \pm 0.55$	$3.53^{Aa} \pm 1.12$	$2.47^{Bb} \pm 0.56$	$2.55^{Ab} \pm 0.65$
EsISO	$2.32^{Ab} \pm 0.59$	$4.18^{Aa} \pm 1.40$	$3.08^{Aa} \pm 1.08$	$2.78^{Ab} \pm 0.55$	$2.55^{Bb} \pm 0.29$	$2.67^{Ab} \pm 0.50$
LR IV	$1.85^{Ab} \pm 0.41$	$4.73^{Aa} \pm 0.58$	$3.95^{Aa} \pm 0.53$	$3.58^{Aa} \pm 0.62$	$3.52^{Ab} \pm 0.53$	$2.58^{Ab} \pm 0.62$
Serum creatinine						
EsHYPO	$1.27^{Ac} \pm 0.12$	$1.92^{Aa} \pm 0.15$	$1.65^{Ab} \pm 0.16$	$1.67^{Ab} \pm 0.22$	$1.55^{Ab} \pm 0.08$	$1.28^{Ac} \pm 0.17$
EsISO	$1.28^{Ac} \pm 0.18$	$1.95^{Aa} \pm 0.18$	$1.65^{Ab} \pm 0.32$	$1.63^{Ab} \pm 0.27$	$1.43^{Ab} \pm 0.34$	$1.25^{Ac} \pm 0.31$
LR IV	$1.10^{Ac} \pm 0.13$	$1.82^{Aa} \pm 0.12$	$1.43^{Bb} \pm 0.15$	$1.32^{Bb} \pm 0.16$	$1.32^{Ab} \pm 0.19$	$1.22^{Ac} \pm 0.17$
Plasma glucose						
EsHYPO	$96.00^{Ac} \pm 5.10$	$111.17^{Ab} \pm 15.00$	$149.00^{Ba} \pm 20.99$	$142.33^{Ba} \pm 11.36$	$120.33^{Ba} \pm 10.58$	$102.17^{Ac} \pm 18.71$
EsISO	$92.50^{Ac} \pm 5.68$	$104.67^{Ab} \pm 11.15$	$178.50^{Aa} \pm 22.12$	$184.83^{Aa} \pm 29.94$	$148.17^{Aa} \pm 28.53$	$117.17^{Ac} \pm 21.49$
LR IV	$90.83^{Ac} \pm 5.04$	$101.83^{Aa} \pm 7.83$	$97.83^{Ca} \pm 5.04$	$97.67^{Ca} \pm 3.14$	$99.33^{Bb} \pm 3.93$	$104.50^{Aa} \pm 7.34$
Serum osmolarity						
EsHYPO	$266.50^{Ab} \pm 16.84$	$280.00^{Aa} \pm 13.49$	xxx	$271.00^{Ab} \pm 11.59$	xxx	$269.50^{Ab} \pm 10.60$
EsISO	$269.83^{Ab} \pm 7.91$	$279.00^{Aa} \pm 3.41$	xxx	$271.00^{Ab} \pm 6.87$	xxx	$271.83^{Ab} \pm 5.12$
LR IV	$270.17^{Ab} \pm 12.51$	$281.33^{Aa} \pm 9.91$	xxx	$277.00^{Ab} \pm 6.96$	xxx	$273.50^{Ab} \pm 7.12$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < .05$).

TABLE 4 | Means and standard deviations of urinary sodium (mmol L^{-1}), potassium (mmol L^{-1}), chloride (mmol L^{-1}), urinary calcium (mg dl^{-1}) and magnesium (mg dl^{-1}) in horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities.

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Urinary sodium						
EsHYPO	$13.33^{Ab} \pm 11.78$	$42.33^{Aa} \pm 38.09$	$22.50^{Aa} \pm 29.15$	$8.00^{Bb} \pm 11.63$	$6.17^{Bb} \pm 8.28$	$14.17^{Bb} \pm 11.55$
EsISO	$14.33^{Ab} \pm 19.33$	$47.50^{Aa} \pm 41.13$	$20.33^{Aa} \pm 34.45$	$16.33^{Bb} \pm 26.70$	$21.17^{Bb} \pm 26.12$	$21.17^{Bb} \pm 28.92$
LR IV	$8.17^{Ac} \pm 6.24$	$61.00^{Ab} \pm 39.51$	$59.33^{Ab} \pm 69.40$	$106.67^{Aa} \pm 70.67$	$153.67^{Aa} \pm 28.39$	$140.83^{Aa} \pm 36.5$
Urinary potassium						
EsHYPO	$90.83^{Ab} \pm 97.66$	$206.67^{Aa} \pm 173.97$	$157.17^{Aa} \pm 138.21$	$49.50^{Bb} \pm 61.41$	$22.83^{Ab} \pm 26.03$	$14.00^{Ac} \pm 4.82$
EsISO	$96.17^{Ab} \pm 100.62$	$171.00^{Aa} \pm 95.79$	$114.00^{Aa} \pm 66.14$	$74.17^{Bb} \pm 53.17$	$34.00^{Ab} \pm 25.64$	$12.50^{Ac} \pm 8.31$
LR IV	$84.00^{Ab} \pm 89.02$	$194.00^{Aa} \pm 162.36$	$128.67^{Aa} \pm 110.64$	$120.33^{Aa} \pm 94.80$	$34.67^{Aa} \pm 27.08$	$10.00^{Ac} \pm 4.34$
Urinary chloride						
EsHYPO	$96.67^{Aa} \pm 45.34$	$31.67^{Ab} \pm 20.78$	$27.00^{Ab} \pm 14.89$	$25.50^{Ab} \pm 17.63$	$25.17^{Bb} \pm 23.57$	$26.17^{Bb} \pm 8.47$
EsISO	$97.17^{Aa} \pm 24.29$	$29.17^{Ab} \pm 26.66$	$38.67^{Ab} \pm 16.52$	$50.33^{Ab} \pm 32.28$	$51.50^{Ab} \pm 29.32$	$37.00^{Bb} \pm 24.50$
LR IV	$81.67^{Ab} \pm 70.01$	$27.00^{Ac} \pm 24.86$	$31.00^{Ac} \pm 23.14$	$36.17^{Ac} \pm 28.10$	$71.67^{Ab} \pm 29.40$	$102.67^{Aa} \pm 44.47$
Urinary calcium						
EsHYPO	$40.15^{Aa} \pm 9.28$	$20.20^{Ab} \pm 16.09$	$11.15^{Ab} \pm 4.08$	$15.90^{Ab} \pm 14.55$	$23.57^{Ab} \pm 12.75$	$7.77^{Ac} \pm 3.89$
EsISO	$37.58^{Aa} \pm 6.36$	$21.30^{Ab} \pm 12.28$	$24.20^{Ab} \pm 15.02$	$19.98^{Ab} \pm 16.28$	$14.68^{Ab} \pm 3.78$	$7.72^{Ac} \pm 5.95$
LR IV	$35.28^{Aa} \pm 13.46$	$21.47^{Ab} \pm 5.91$	$13.45^{Ab} \pm 3.98$	$5.67^{Bc} \pm 4.26$	$6.13^{Bc} \pm 2.67$	$4.87^{Bc} \pm 1.13$
Urinary magnesium						
EsHYPO	$2.96^{Ab} \pm 1.44$	$4.67^{Aa} \pm 1.97$	$6.29^{Aa} \pm 2.08$	$5.99^{Aa} \pm 2.04$	$6.58^{Aa} \pm 1.75$	$4.81^{Ab} \pm 2.95$
EsISO	$4.20^{Ab} \pm 1.44$	$5.33^{Aa} \pm 0.92$	$4.88^{Aa} \pm 1.50$	$6.07^{Aa} \pm 0.88$	$5.22^{Aa} \pm 1.07$	$3.52^{Ab} \pm 0.87$
LR IV	$2.87^{Ab} \pm 1.74$	$5.08^{Aa} \pm 0.77$	$3.12^{Bb} \pm 1.11$	$3.90^{Ab} \pm 1.07$	$3.32^{Bb} \pm 1.46$	$1.62^{Bc} \pm 0.66$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < 0.05$).

TABLE 5 | Means and standard deviations of urinary urea (mg dl^{-1}), creatinine (mg dl^{-1}) and glucose (mg dl^{-1}) in horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities.

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Urinary urea						
EsHYPO	$156.83^{Ac} \pm 46.24$	$410.50^{Ba} \pm 16.90$	$370.50^{Ba} \pm 47.93$	$269.50^{Bb} \pm 73.24$	$218.33^{Bb} \pm 61.70$	$146.00^{Ac} \pm 59.90$
EsISO	$172.83^{Ab} \pm 73.89$	$477.83^{Ba} \pm 71.72$	$374.00^{Ba} \pm 150.23$	$354.67^{Ba} \pm 107.49$	$314.00^{Ba} \pm 81.20$	$172.17^{Ab} \pm 38.84$
LR IV	$224.33^{Ab} \pm 104.24$	$627.67^{Aa} \pm 55.01$	$628.17^{Aa} \pm 63.36$	$606.17^{Aa} \pm 100.78$	$467.50^{Aa} \pm 170.17$	$166.67^{Ab} \pm 92.07$
Urinary creatinine						
EsHYPO	$39.58^{Ab} \pm 29.93$	$472.50^{Aa} \pm 119.25$	$437.50^{Aa} \pm 241.52$	$236.67^{Aa} \pm 123.59$	$33.07^{Bb} \pm 26.26$	$10.83^{Ac} \pm 8.61$
EsISO	$39.17^{Ab} \pm 35.97$	$340.42^{Aa} \pm 123.99$	$221.25^{Aa} \pm 79.13$	$225.00^{Aa} \pm 90.80$	$85.00^{Ab} \pm 53.22$	$21.67^{Ab} \pm 20.17$
LR IV	$39.58^{Ab} \pm 54.28$	$347.08^{Aa} \pm 112.79$	$282.92^{Aa} \pm 124.98$	$212.92^{Aa} \pm 147.72$	$37.05^{Bb} \pm 18.24$	$8.75^{Ac} \pm 6.85$
Urinary glucose						
EsHYPO	$0.00^{Ab} \pm 0.00$	$0.00^{Ab} \pm 0.00$	$0.00^{Bb} \pm 0.00$	$0.33^{Ba} \pm 0.82$	$0.00^{Bb} \pm 0.00$	$0.17^{Ba} \pm 0.41$
EsISO	$0.00^{Ac} \pm 0.00$	$0.00^{Ac} \pm 0.00$	$0.17^{Ab} \pm 0.41$	$1.00^{Aa} \pm 1.26$	$1.17^{Aa} \pm 1.33$	$0.33^{Ab} \pm 0.52$
LR IV	$0.00^{Aa} \pm 0.00$	$0.00^{Aa} \pm 0.00$	$0.00^{Ba} \pm 0.00$	$0.00^{Ca} \pm 0.00$	$0.00^{Ca} \pm 0.00$	$0.00^{Ca} \pm 0.00$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < 0.05$).

TABLE 6 | Means and standard deviations of urinary volume (ml), pH and specific gravity in horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities.

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Urinary volume						
EsHYPO			$110.00^{Ad} \pm 67.90$	$1376.67^{Ac} \pm 1163.9$	$3095.8^{Ab} \pm 2296.51$	$6611.6^{Ba} \pm 2384.28$
EsISO			$97.50^{Ad} \pm 73.06$	$675.00^{Ac} \pm 413.22$	$1950.0^{Ab} \pm 1017.84$	$5785.8^{Ba} \pm 2036.25$
LR IV			$135.00^{Ad} \pm 63.48$	$836.67^{Ac} \pm 900.81$	$2100.0^{Ab} \pm 1764.55$	$10775^{Aa} \pm 4534.29$
Urinary pH						
EsHYPO	$7.25^{Aa} \pm 1.08$	$7.50^{Aa} \pm 1.18$	$7.83^{Aa} \pm 1.13$	$7.58^{Ba} \pm 1.02$	$7.50^{Ba} \pm 0.89$	$7.00^{Aa} \pm 1.22$
EsISO	$7.25^{Aa} \pm 0.88$	$7.58^{Aa} \pm 0.97$	$7.83^{Aa} \pm 0.98$	$7.75^{Ba} \pm 0.94$	$7.42^{Ba} \pm 0.97$	$7.08^{Aa} \pm 0.92$
LR IV	$7.42^{Ab} \pm 1.11$	$7.50^{Ab} \pm 1.18$	$7.50^{Ab} \pm 1.18$	$8.08^{Aa} \pm 1.07$	$8.33^{Aa} \pm 0.41$	$7.67^{Ab} \pm 1.03$
Specific gravity						
EsHYPO	$1010.0^{Ab} \pm 6.81$	$1031.6^{Aa} \pm 7.74$	$1030.0^{Aa} \pm 12.52$	$1019.3^{Aa} \pm 14.57$	$1007.0^{Ab} \pm 4.86$	$1004.1^{Ab} \pm 2.86$
EsISO	$1007.6^{Ac} \pm 6.12$	$1025.0^{Aa} \pm 10.64$	$1025.6^{Aa} \pm 8.62$	$1026.3^{Aa} \pm 5.13$	$1013.0^{Ab} \pm 7.35$	$1004.0^{Ac} \pm 2.53$
LR IV	$1007.6^{Ac} \pm 4.46$	$1031.0^{Aa} \pm 11.71$	$1025.6^{Aa} \pm 8.71$	$1024.6^{Aa} \pm 11.15$	$1016.0^{Ab} \pm 12.46$	$1005.6^{Ac} \pm 2.94$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < 0.05$).

has been described that LRS solution does not have an adequate concentration of calcium (15). Since calcium is naturally excreted in horses' urine, its supplementation is necessary when using LRS intravenously, especially in long-term fluid therapy and in patients who are not eating. The EsHYPO and EsISO enteral solutions had significant amounts of calcium acetate ($1g.L^{-1}$). This justifies the effectiveness of these solutions in reversing the decrease in serum ionized calcium caused by the DP. Urinary calcium excretion decreased at T0h ($P < 0.05$) and remained low throughout the fluid therapy phase in the EsHYPO and EsISO groups. Although lower than baseline, values were significantly higher than those of the LR IV treatment, demonstrating the effect of higher calcium concentration in the enteral electrolyte solutions.

Serum magnesium increased after the DP ($P < 0.05$) likely due to renal compensatory mechanisms that acted to preserve it in exchange for the excretion of cations stimulated by furosemide. All three treatments reversed this increase by replacing blood volume, however, in the LR IV group there was a marked and gradual decrease in this electrolyte, reaching its lowest value at T8h (**Table 2**). This is justified by the absence of magnesium sources in LRS and by hemodilution. The absence of magnesium in LRS also explains its lower urinary excretion in the LR IV treatment group in comparison to both enteral fluids (**Table 4**). A slight decrease in serum magnesium was observed in both enteral electrolyte treatment groups despite the addition of this electrolyte in their composition. This was possibly due to hemodilution and the amount of magnesium chloride contained in both solutions, as mentioned by Ribeiro Filho et al. (5). Although low, this change was significantly milder when compared with the LR IV group. Urinary magnesium at some time points during the fluid therapy

TABLE 7 | Means and standard deviations of blood pH, $cHCO_3^-$ (mmol L^{-1}), pCO_2 (mmHg), Base Excess (BE) (mmol L^{-1}), Strong Ions Difference (SID) (mEq L^{-1}) and Anion Gap (AG) (mEq L^{-1}) of horses submitted to water and food restriction and treated in a 6 × 3 crossover design with different hydroelectrolytic therapy modalities..

Treatment	Time					
	(-)36 h	0 h	2 h	4 h	6 h	8 h
Blood pH						
EsHYPO	$7.41^{Ab} \pm 0.02$	$7.43^{Aa} \pm 0.02$	$7.39^{Ac} \pm 0.02$	$7.37^{Ac} \pm 0.02$	$7.37^{Ac} \pm 0.02$	$7.36^{Bc} \pm 0.03$
EsISO	$7.41^{Ab} \pm 0.02$	$7.45^{Aa} \pm 0.02$	$7.39^{Ac} \pm 0.03$	$7.36^{Ad} \pm 0.03$	$7.35^{Ad} \pm 0.04$	$7.33^{Bd} \pm 0.04$
LR IV	$7.40^{Ab} \pm 0.02$	$7.43^{Aa} \pm 0.02$	$7.41^{Ab} \pm 0.03$	$7.39^{Ab} \pm 0.03$	$7.39^{Ab} \pm 0.02$	$7.39^{Ab} \pm 0.02$
$cHCO_3^-$						
EsHYPO	$27.48^{Ab} \pm 2.37$	$30.82^{Aa} \pm 2.45$	$27.88^{Ab} \pm 3.10$	$26.25^{Ab} \pm 2.66$	$24.85^{Ac} \pm 2.31$	$23.85^{Bc} \pm 2.07$
EsISO	$28.67^{Ab} \pm 1.89$	$32.58^{Aa} \pm 1.77$	$28.93^{Aa} \pm 2.40$	$26.02^{Ac} \pm 2.19$	$24.28^{Ac} \pm 2.56$	$23.43^{Bc} \pm 2.91$
LR IV	$27.82^{Ab} \pm 1.83$	$29.45^{Aa} \pm 2.38$	$29.13^{Ab} \pm 2.91$	$26.48^{Ab} \pm 1.20$	$26.05^{Ab} \pm 0.83$	$27.40^{Ab} \pm 1.85$
PCO_2						
EsHYPO	$43.30^{Aa} \pm 2.73$	$45.70^{Aa} \pm 2.07$	$46.02^{Aa} \pm 4.23$	$44.47^{Aa} \pm 3.70$	$42.78^{Aa} \pm 3.71$	$41.90^{Aa} \pm 3.19$
EsISO	$44.47^{Ab} \pm 1.89$	$47.05^{Aa} \pm 1.97$	$46.75^{Ab} \pm 1.84$	$45.38^{Ab} \pm 2.10$	$43.43^{Ab} \pm 1.99$	$44.07^{Ab} \pm 2.32$
LR IV	$44.48^{Aa} \pm 1.87$	$44.33^{Aa} \pm 1.94$	$45.32^{Aa} \pm 4.42$	$43.45^{Aa} \pm 1.55$	$42.78^{Aa} \pm 2.44$	$44.82^{Aa} \pm 2.55$
BE						
EsHYPO	$2.67^{Aa} \pm 2.73$	$6.67^{Ba} \pm 2.73$	$3.17^{Aa} \pm 3.31$	$1.17^{Ab} \pm 2.99$	$-0.33^{Ab} \pm 2.50$	$-1.50^{Aa} \pm 2.43$
EsISO	$4.00^{Ab} \pm 2.19$	$9.17^{Aa} \pm 1.83$	$4.17^{Ab} \pm 2.86$	$0.67^{Ac} \pm 2.50$	$-1.17^{Ac} \pm 3.31$	$-2.33^{Ab} \pm 3.44$
LR IV	$2.67^{Aa} \pm 1.86$	$6.00^{Ba} \pm 1.55$	$4.50^{Aa} \pm 3.21$	$1.67^{Ac} \pm 1.63$	$1.17^{Ac} \pm 0.98$	$2.33^{Aa} \pm 1.75$
SID						
EsHYPO	$39.80^{Ab} \pm 1.72$	$41.72^{Aa} \pm 2.48$	$36.88^{Bc} \pm 2.73$	$36.58^{Bc} \pm 1.43$	$31.18^{Bd} \pm 2.71$	$36.77^{Ac} \pm 0.72$
EsISO	$37.30^{Ab} \pm 2.99$	$41.33^{Aa} \pm 5.93$	$35.87^{Bb} \pm 1.85$	$33.90^{Cc} \pm 2.47$	$34.23^{Bc} \pm 2.07$	$32.85^{Bc} \pm 1.99$
LR IV	$37.57^{Ab} \pm 4.22$	$43.30^{Aa} \pm 3.46$	$40.67^{Aa} \pm 2.42$	$39.98^{Aa} \pm 4.14$	$40.55^{Aa} \pm 3.60$	$37.48^{Aa} \pm 3.38$
AG						
EsHYPO	$12.32^{Aa} \pm 2.42$	$10.90^{Ab} \pm 2.94$	$9.00^{Ab} \pm 1.47$	$10.33^{Ab} \pm 2.63$	$6.33^{Ac} \pm 2.64$	$12.92^{Aa} \pm 2.32$
EsISO	$8.63^{Aa} \pm 1.81$	$8.75^{Aa} \pm 4.66$	$6.93^{Bc} \pm 2.17$	$7.88^{Bc} \pm 1.61$	$9.95^{Bb} \pm 2.73$	$9.42^{Ab} \pm 1.69$
LR IV	$9.75^{Ac} \pm 3.96$	$13.85^{Ab} \pm 3.41$	$11.53^{Cb} \pm 2.60$	$13.50^{Cb} \pm 3.74$	$14.50^{Ca} \pm 3.58$	$10.08^{Ac} \pm 4.05$

Average values followed by different capital letters in the same column or by different lowercase letters in the same line differ according to Tukey's test ($P < 0.05$).

phase with EsHypo and EsISO reached values above baseline (T-36h). This constitutes an advantage in the administration of enteral electrolyte solutions containing magnesium, especially in patients with hypomagnesaemia.

Serum phosphorus showed different behavior for each experimental group, since neither enteral solutions nor LRS contain this element. Therefore, the dynamics of its values are due to the hemodilution caused by fluid replacement as observed by Ribeiro Filho et al. (16, 17), associated with natural endocrine mechanisms of organic phosphorus regulation (1).

In the present study, both urea and creatinine increased after the DP demonstrating decreased blood volume and glomerular filtration rate, even though values did not exceed the reference intervals for the species (8). Thus, the DP was able to promote dehydration in the mares without causing pre-renal azotemia (14). Urea and creatinine values progressively regressed to baseline after 8 h of treatment in all experimental groups, demonstrating similar efficacy in restoring blood volume, tissue perfusion and glomerular filtration. However, LR IV treatment was more effective in decreasing creatinine values faster than both enteral electrolyte treatments (T2h and T4h) (**Table 3**). This result shows that the administration of electrolyte solutions intravenously expands blood volume quickly, promoting the excretion of undesirable metabolites. However, from T6h on, both enteral electrolyte solutions had the same effect as the RL IV group. The dynamics of urinary urea and creatinine levels reflected a marked urine concentration in the DP. All treatments, although in different ways, were able to dilute urine throughout the hydration period (**Table 5**). The dynamics of urinary urea and creatinine values proved the efficacy of enteral fluid therapy in continuous flow (EFTcf) compared to LR IV treatment in correcting urine concentration. Similar results have been observed after 12 h of EFTcf at similar infusion rates in horses (5).

In the present study, plasma lactate values significantly increased after the DP ($P < 0.05$), confirming decreased blood volume and tissue perfusion. All three treatments were similarly effective in bringing lactate levels back to baseline, demonstrating equivalent efficacy in promoting volume expansion and tissue perfusion (**Table 3**). The effect of different formulations of EFTcf in reducing serum lactate in horses by expanding plasma volume and promoting tissue perfusion has been previously reported (17).

The DP promoted a significant increase in plasma glucose in all three treatment groups ($P < 0.05$). This can be attributed to fasting, which induces gluconeogenesis by recruiting body energy reserves (18) and by the stress promoted by the DP (19). Glucose behaved differently in all three treatment groups during the

fluid therapy phase, which can be explained by the formulation of each solution. LRS has no energy sources, thus the LR IV group demonstrated significantly lower blood glucose during the hydration phase when compared to the EsISO and EsHYPO groups, but still within the normal range. EsISO and EsHYPO groups had significantly higher values of plasma glucose, specially EsISO when compared to EsHYPO (**Table 3**). This difference can be justified by the greater amount of energy sources in the EsISO formulation. Results demonstrated the action of glycemic regulatory mechanisms in all groups. The efficacy in restoring glycemia of enteral solutions associated with highly metabolizable energy sources has been previously observed in studies that compared them to other types of fluid therapies such as LRS (6) and that evaluated different formulations of EFTcf (17). Thus, in the current experimental design, the addition of energy sources in enteral solutions formulations for hydroelectrolytic therapy in horses is advantageous over LR IV therapy.

The dynamics of serum osmolarity values illustrate plasma expansion and blood volume restauration in the different fluid therapy modalities studied. All three treatments were efficient in reversing the increase in serum osmolarity that occurred due to food and water deprivation and water loss induced by the DP, leading to higher concentrations of serum solutes. There was a decrease in serum osmolarity values during the hydration phase, but at T8h values remained similar to baseline (**Table 3**). This was considered an advantage, since the main concern with the use of hypotonic enteral electrolyte solutions in horses is the decrease in serum osmolarity. The application of hypotonic enteral electrolyte solutions has already been tested in several animal species without triggering this adverse effect (4, 5, 20).

All treatments promoted an increase in urinary volume starting at T2h, accompanied by changes in urinary color from dark amber at T2h and T4h to a clear, translucent and limpid urine at T6h and T8h. The LR IV treatment promoted significantly greater urination volume when compared to the EsISO and EsHYPO treatments. This difference is justified by the fact that the LR IV treatment is administered directly into the vascular bed, which increases its speed and capacity to promote blood volume expansion and glomerular filtration rate. In addition, it stimulates the release of the atrial natriuretic peptide and all these mechanisms translate into large volumes of urine (1). This can be seen as an advantage of LR IV therapy, especially in the replacement phase of a therapeutic fluid therapy plan. Nevertheless, this significantly higher urine volume demonstrates that the IV fluids are excreted shortly after administration, not allowing time for the transfer of fluids from the vascular compartment to the tissues and the intracellular compartment, which is the main objective when hydrating an equine patient (21). Therapies with enteral electrolyte solutions also induced urination, but in significantly smaller volumes. Since the administered volumes of electrolyte solutions were equivalent between EsISO, EsHYPO and LR IV groups, the smaller amount of urine excreted demonstrates that EFTcf, in addition to blood volume expansion and increase in glomerular filtration rate, allows greater retention of the administered fluids. This may yield better distribution of water and electrolytes into tissues, intracellular compartments and also the rehydration of ingesta. EFTcf's ability to promote diuresis was also reported by Monteiro et al. (4) and Ribeiro Filho et al. (5).

No changes in urinary pH were observed after the DP and within the EsISO and EsHYPO treatment groups during the fluid therapy phase. Urinary pH was significantly higher in the RL IV group in comparison to both EFTcf at T4h and T6h (**Table 6**), but values remained in the normal range (22). Mild aciduria was previously described in horses treated with different EFTcf formulations due to renal mechanisms to control the acid-base balance, mainly by the renal excretion of H^+ ions (3).

Urinary specific gravity, a sensitive marker of blood volume, increased as a consequence of the DP ($P < 0.05$), but all three treatments were similarly effective to promote the production of diluted urine, leading to hypostenuria at the end of the 8-h hydration period. The dynamics of urinary specific gravity values observed here confirms the effectiveness of EFTcf therapies compared to LR IV treatment in restoring hydration. Other studies showed similar findings in horses treated with different formulations of enteral fluid therapies (3–5).

Groups treated with enteral electrolyte solutions, which have the addition of energy sources, presented mild glycosuria at a few time points. This finding was more remarkable in EsISO, which had a higher glycide content. According to Wilson (14), the presence of glucose in urine reflects an overload on renal function's ability to reabsorb filtered blood glucose and can occur with the use of fluid therapies with carbohydrate excess (5). Since the glycosuria observed in the present study was discrete (14) it was not considered clinically relevant (**Table 5**).

The DP caused an increase in pH, HCO_3^- and BE (**Table 7**). This was determined by the chloride depressant action of furosemide, as reported by Freestone et al. (23) and Alves et al. (15), who also used this drug in the experimental induction of hydroelectrolytic and acid-base imbalances in horses. The excretion of chloride is compensated by the retention of bicarbonate, which justifies the changes observed. Depending on the posology furosemide may cause hypochloremic metabolic alkalosis. All treatments were able to reverse the changes mentioned above, however the EsISO and EsHYPO treatment groups reached the lowest pH, HCO_3^- and BE levels at T8h when compared to T-36h. This effect was not observed in the LR IV group (**Table 7**).

The energy source of EsHYPO and EsISO treatments may have been the cause of the slight decrease in blood pH, HCO_3^- and BE observed. As mentioned by Gomes et al. (24), the addition of carbohydrates in enteral solutions can lead to intestinal microbial fermentation and the production of organic acids, that are absorbed and might generate this effect. Even so, it is necessary to highlight that the effect of enteral electrolyte solutions on the referred variables was mild, especially in the EsHYPO group. In addition, none of the animals treated with enteral electrolyte solutions showed any signs or complications related to these findings. The small acidifying effect observed in the EsISO group makes this solution an option for dehydrated horses with mild metabolic alkalosis.

No significant changes in pH, HCO_3^- and BE were detected during the hydration period in LR IV treatment group. Since Lactate Ringer's solution has a similar composition to plasma it

does not have an alkalizing or acidifying effect. Corroborating this fact, it was observed that the intravenous use of LRS in a volume of 10% of body weight for a 6-h treatment in healthy horses did not induce changes in acid-base balance (25). Likewise, daily volumes of 12 to 19% of body weight of intravenous lactate Ringer's solution infused in horses submitted to experimental induction of colonic impaction had no significant effect on the acid base balance (26).

PCO_2 values were significantly increased in the EsISO group at T0h ($P < 0.05$), which characterizes the development of respiratory compensatory activity. Although minor, according to Hinchcliff et al. (27) it already expresses mild respiratory acidosis. At T0h BE demonstrated low-intensity metabolic alkalosis (9.17 mmol L^{-1}), so the respiratory system compensates with respiratory acidosis (28). During the fluid therapy period, secondary or compensatory respiratory acidosis resolved with pCO_2 values returning to baseline at T8h (**Table 7**). In the EsHYPO and LR IV treatments, pCO_2 remained unchanged throughout experimental phase ($P > 0.05$) confirming that both did not cause changes that required compensation in the acid-base balance.

The anion gap showed little variation throughout the experimental period and values remained in the normal range (24, 26) in all three treatment groups. SID remained unchanged in the LR IV treatment group during the fluid therapy period and at the lower limit in EsHYPO. EsISO contains more chloride than the other solutions, therefore it promoted the greatest decrease in SID values at T8h, revealing metabolic acidosis.

Enteral solutions can be used in horses as maintenance fluid therapy, especially given its physiological route of administration and its low cost, it also can be manipulated according to the patient needs. The use of LR IV is still necessary in cases where the horse has reflux, intestinal obstruction and when it is not able to stand. EsHYPO is a good maintenance choice for long term fluid therapy, while EsISO would be better used as treatment for mild alkalosis.

CONCLUSION

The present study demonstrated the efficacy and safety of enteral fluid therapy with isotonic and hypotonic electrolyte solution administered in continuous flow in the replacement of blood volume in horses when compared to intravenous fluid therapy with lactated Ringer's solution (RL IV). Hypotonic enteral solution (EsHYPO) and lactated Ringer's solution (RL IV) can be used in long-term fluid therapy. Since it has a slightly acidifying effect, the isotonic enteral solution (EsISO) could be an option in the treatment of low-intensity metabolic alkalosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Use Ethics Committee of Universidade Federal de Viçosa (UFV).

AUTHOR CONTRIBUTIONS

DD, JR, TB, and RV were responsible for the conception of the study, data analysis, and provided intellectual input on the manuscript. DD, JR, NM, FD, SA, and PS were responsible for carrying out the experimental phase of the study. DD, JR, RT, HM, and NM were responsible for data interpretation and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Veterinary Science

REVIEW
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Intravenous and Oral Fluid Therapy in Neonatal Calves With Diarrhea or Sepsis and in Adult Cattle

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Optimal fluid therapy protocols in neonatal calves and adult cattle are based on consideration of signalment, history, and physical examination findings, and individually tailored whenever laboratory analysis is available. Measurement of the magnitude of eye recession, duration of skin tenting in the lateral neck region, and urine specific gravity by refractometry provide the best estimates of hydration status in calves and cattle. Intravenous and oral electrolyte solutions (OES) are frequently administered to critically ill calves and adult cattle. Application of physicochemical principles indicates that 0.9% NaCl, Ringer's solution, and 5% dextrose are equally acidifying, lactated Ringer's and acetated Ringer's solution are neutral to mildly acidifying, and 1.3–1.4% sodium bicarbonate solutions are strongly alkalinizing in cattle. Four different crystalloid solutions are recommended for intravenous fluid therapy in dehydrated or septic calves and dehydrated adult cattle: (1) lactated Ringer's solution and acetated Ringer's solution for dehydrated calves, although neither solution is optimized for administration to neonatal calves or adult cattle; (2) isotonic (1.3%) or hypertonic (5.0 or 8.4%) solutions of sodium bicarbonate for the treatment of calves with diarrhea and severe strong ion (metabolic) acidosis and hyponatremia, and adult cattle with acute ruminal acidosis; (3) Ringer's solution for the treatment of metabolic alkalosis in dehydrated adult cattle, particularly lactating dairy cattle; and (4) hypertonic NaCl solutions (7.2%) and an oral electrolyte solution or water load for the rapid resuscitation of dehydrated neonatal calves and adult cattle. Much progress has been made since the 1970's in identifying important attributes of an OES for diarrheic calves. Important components of an OES for neonatal calves are osmolality, sodium concentration, the effective SID that reflects the concentration of alkalinizing agents, and the energy content. The last three factors are intimately tied to the OES osmolality and the abomasal emptying rate, and therefore the rate of sodium delivery to the small intestine and ultimately the rate of resuscitation. An important need in fluid and electrolyte therapy for adult ruminants is formulation of a practical, effective, and inexpensive OES.

Keywords: osmolality, alkalosis, acidosis, fluid therapy, acid–base balance, oral electrolyte solution

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INTRODUCTION

Intravenous solution formulations should be optimized for different species (1) and fluid therapy should be patient-centered and not follow a "one fluid for all" principle (2). Five abnormalities can concurrently exist in critically ill neonatal calves and adult cattle: (a) free water deficit; (b) abnormal plasma electrolyte concentrations; (c) acid–base abnormalities; (d) plasma osmolality abnormalities; and (e) plasma oncotic pressure imbalances. Optimal fluid therapy protocols in neonatal calves and adult cattle are based on consideration of signalment, history, and physical examination findings, and should be individually tailored if laboratory analysis is available. The signalment, history, and clinical diagnosis will suggest the likely presence of decreased free water volume and abnormalities in plasma electrolyte concentrations, acid-base balance, osmolality and oncotic pressure. Serum biochemical analysis, particularly measurement of the plasma total CO_2, chloride, sodium, potassium, and calcium concentrations is recommended to optimize fluid therapy in critically ill adult cattle, with the addition of acid-base analysis in critically ill neonatal calves. Unfortunately, most critically ill neonatal calves and adult cattle are treated in resource poor environments on the farm without ready access to laboratory analysis. In these circumstances the clinician determines the nature and degree of the abnormalities likely to be present based on the animal's clinical presentation (3) and uses the information to select the most appropriate intravenous fluid formulation for treatment.

Textbook dogma has long promulgated the belief that only moderate to marked dehydration can be clinically detected in domestic animals. Experimental studies have demonstrated that mild dehydration can be readily detected in neonatal calves, in that a dehydration of 2% body weight is associated with slight enophthalmos of 1 mm, dry mucous membranes, and a prolonged skin tent duration to 3 s (4). Dehydration (percent body weight) can be accurately quantified in neonatal calves by multiplying the degree of eye recession into the orbit in mm by 1.6 [**Figure 1**; (4)]. It is not known whether a similar relationship exists for adult cattle. Measurement of urine specific gravity by refractometry is also clinically helpful in assessing urine osmolality and therefore free water balance [**Figure 2**; (5)]. Urine color has moderate clinical utility for assessing urine osmolality in cattle (**Figure 3**), but measurement of urine specific gravity by dipstick is not recommended because it provides an inaccurate measure of urine osmolality (5).

Reductions in cardiac output in dehydrated calves are associated with decreased peripheral perfusion and therefore cooler extremities. Peripheral (fetlock) temperature, and the related core-peripheral temperature difference, can therefore be used to guide the need for intravenous fluid therapy when measured in temperature-controlled surroundings (6). The clinical utility of peripheral temperature as a predictor of the need for intravenous fluid therapy was first investigated in critically ill humans in the 1950's, when it was observed that the prognosis for survival was decreased as the temperature of the big toe approached the ambient room temperature. A portable low cost hand-held infrared thermographic unit provides a quantitative tool to measure the peripheral temperature, particularly the hind fetlocks, of neonatal calves with diarrhea (6). A core-peripheral temperature difference of >13°F (>7°C) in neonatal calves with diarrhea indicated that cardiac output was <65% of the mean value for healthy calves, and after this point hindlimb fetlock temperature decreased with additional reductions in cardiac output (**Figure 4**). Peripheral temperature can also be estimated by using the hand to palpate the hind fetlocks or ears and the perceived temperature compared to the peripheral temperature of healthy calves housed in the same environment (6).

Primary therapeutic objectives of fluid therapy are to correct existing abnormalities and to provide maintenance therapy. Existing abnormalities typically require 4–6 h to correct and maintenance therapy may be needed for 2–4 days (7). The estimated volume required to rehydrate the animal and correct electrolyte and acid-base abnormalities should be given intravenously in the first 4–6 h. The normalization of circulating blood volume will increase renal blood flow and glomerular filtration rate and thereby restore renal function and facilitate the correction of electrolyte and acid–base abnormalities. Other routes of parenteral fluid administration (subcutaneous, intraperitoneal) are inferior to the intravenous route for the rapid resuscitation of critically ill neonatal calves (8) and adult cattle.

The amount of fluid required and route of administration depends on the initial degree of dehydration, and an estimate of the continuous losses that occur during treatment, in conjunction with the animal's maintenance requirements during treatment due to minimal intake of water, electrolytes and nutrients. The total volume of fluid to correct dehydration is calculated based on percent dehydration and body weight (BW). In animals that are sufficiently dehydrated to warrant intravenous fluid therapy, at least 3 to 5 L of intravenous fluid is required in a neonatal calf (8% dehydrated × 50 kg BW), and at least 30–50 L in an adult cow (8% dehydrated × 650 kg BW). As previously mentioned, there are two stages to fluid administration: (1) intravenous hydration/corrective therapy in the first 4–6 h (total volume of 100–150 mL/kg BW); and (2) intravenous or oral maintenance therapy in the following 20–24 h (total volume of 60–150 ml/kg BW/24 h) (8). Practical methods for the placement and maintenance of intravenous catheters (auricular vein, jugular vein) in neonatal calves and adult cattle, techniques for administration of intravenous and oral fluids, and the importance of solution temperature in neonatal calves are described in detail elsewhere (8–11). Intravenous fluids should be warmed before administration as large volume administration of fluids <38°C will cool the calf. However, it must be recognized that even when prewarmed fluids (38°C) are administered that the fluid temperature is decreased below core body temperature when it reaches the calf because solution heat is lost to the environment (12). Fluid warming devices placed around the fluid administration line are efficacious depending on the flow rate, but only when placed as close to the animal as possible (12), which can be challenging in some calves.

Neonatal calves and adult cattle should be monitored during the first hour of intravenous hydration/corrective therapy for evidence of clinical improvement or the development of deleterious effects. The fastest intravenous administration rate of

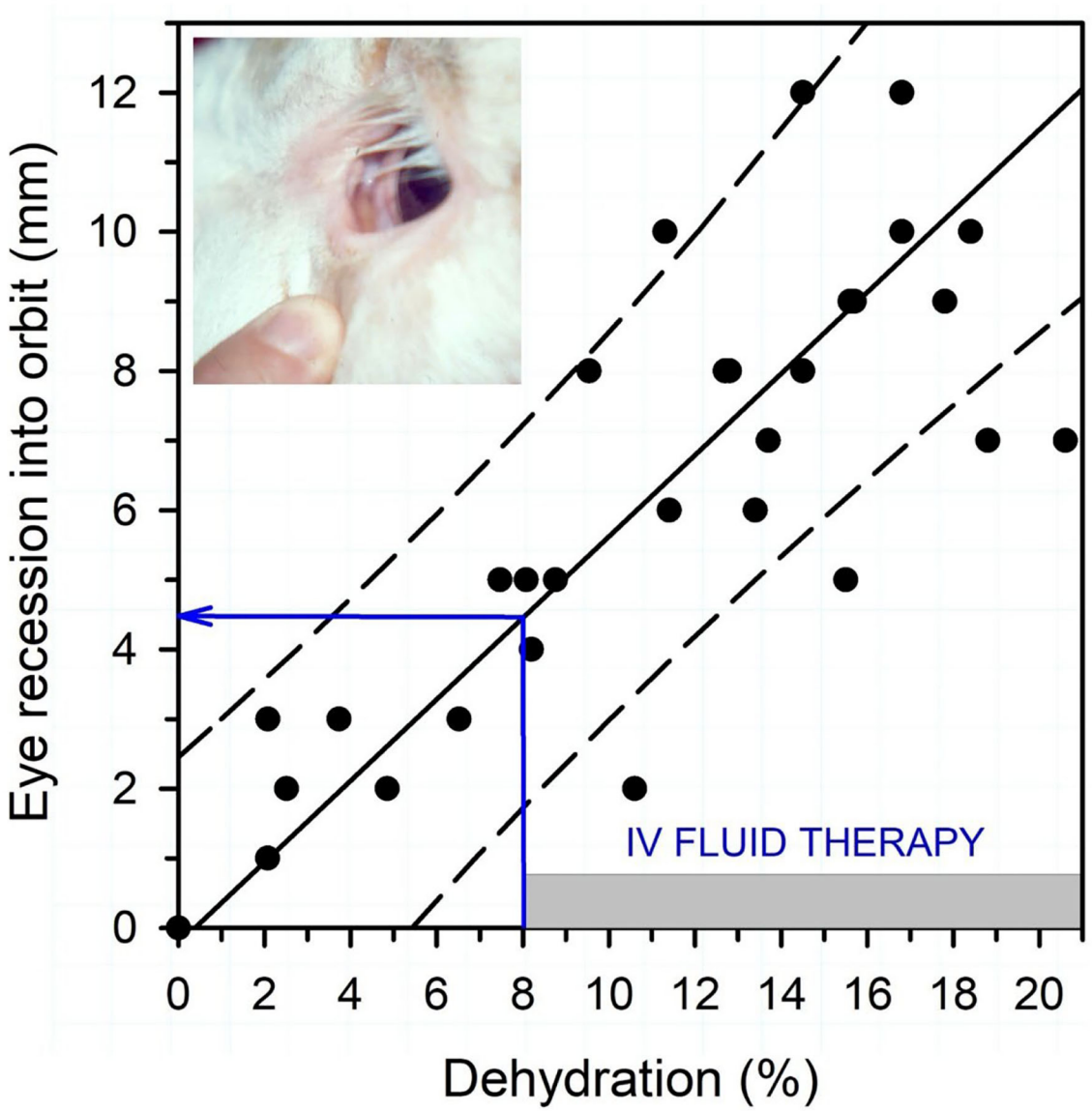

FIGURE 1 | Association between eye recession into the orbit and dehydration (percent body weight) in 15 neonatal calves with experimentally induced diarrhea and dehydration. The filled circles are individual data points (total of 45, 3/calf), the solid line is the linear regression line, and the dashed lines are the 95% confidence interval for prediction. Dehydration (percent of body weight) can be estimated by multiplying the degree of eye recession into the orbit in mm by 1.6. Intravenous fluid administration is recommended when dehydration is estimated at 8% or more of body weight, equivalent to an eye recession into the orbit of 4 mm or more. Figure modified with permission from: Constable et al. (4).

isotonic solutions for resuscitation of critically ill calves in the first hour is 80 ml/kg BW over the first hour of infusion (13), although 50 ml/kg BW has been recommended to minimize the risk of hyperhydration (14). A favorable response in neonatal calves is indicated by an improvement in mental attitude and hydration status within 30–60 min, followed by urination in calves that can stand. Monitoring mean central venous pressure is not practical as sufficiently long catheters are commercially unavailable and technically difficult to place, and because of the large between animal variability in measured central venous pressures (15). Unfavorable responses to treatment include development of a moist cough and tachypnea due to pulmonary edema formation because of a too rapid rate of fluid administration or pre-existing pneumonia and failure to urinate because of acute renal failure. Intravenous fluid administration should be stopped when these clinical signs are observed. The response to intravenous hydration/corrective therapy is slower in adult cattle because fluid administration rates rarely exceed 30 ml/kg BW per hour due to physical constraints related to catheter size and height of the fluid reservoir above the heart (11).

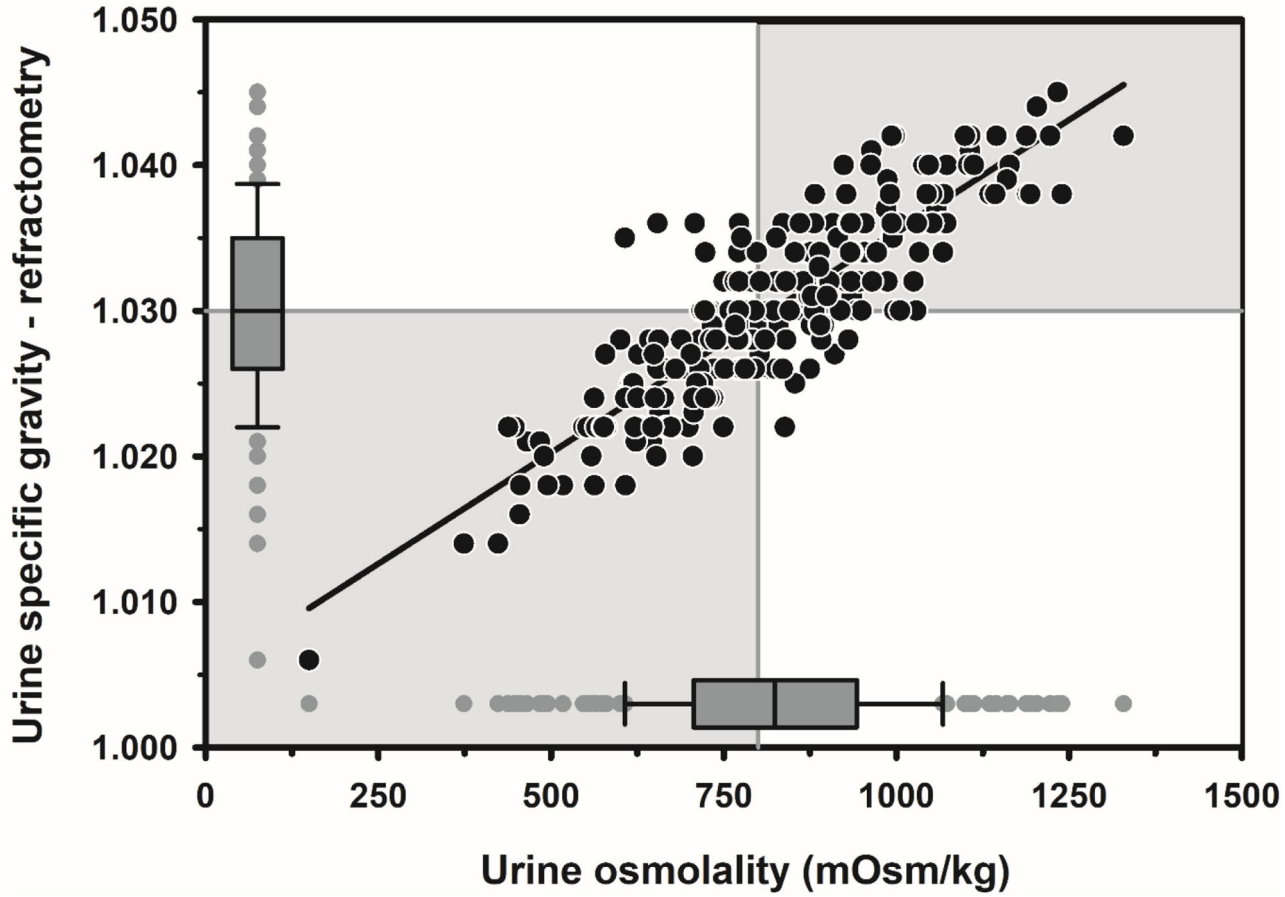

FIGURE 2 | Scatterplot of the linear relationship between urine specific gravity measured by optical refractometry (USG-R) and urine osmolality (UOsm, reference method) for 242 urine samples obtained periodically from 20 multiparous periparturient Holstein-Friesian cows from late gestation to early lactation. Some data points are superimposed. The solid black line is the linear regression line. The solid gray vertical line indicates the recommended threshold value for diagnosing dehydration (UOsm ≥ 800 mOsm/kg), and the solid gray horizontal line indicates the optimal cut point of USG-R (≥ 1.030) identified by logistic regression for diagnosing dehydration. The box and whiskers plots represent the median (middle line), interquartile range (ends of the shaded rectangle), 10% to 90% confidence interval (whiskers), and values outside this confidence interval (small gray circles). Figure modified with permission from: Megahed et al. (5).

Typical intravenous fluid administration rates of 20–30 ml/kg per hour have been recommend for intravenous hydration/corrective therapy in adult cattle (11, 16).

Strong Ion Difference of Plasma, Intravenous Fluids, and Oral Electrolyte Solutions

Fluids can contain charged substances that are positively or negatively charged. Charged substances may have a charge that is fixed and unaltered under physiologic conditions in biological systems, in which case the substances are called strong cations if positively charged, and strong anions if negatively charged. Alternatively, charged substances may have a charge that is variable and dependent on pH under physiologic conditions in biological systems, in which case the substances are called buffer ions, with a net charge varying from positive to zero to negative, depending on the solution pH. Electroneutrality must be preserved; consequently, the sum of the strong cations and positive buffer ions must equal the sum of strong anions and negative buffer ions at a specific pH (17–19).

The strong ion difference (SID) represents the difference between the charge assigned to quantitatively important strong cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and strong anions (Cl^-, L-lactate$^-$, D-lactate$^-$, sulfate^{2-}, ketoacids, non-esterified fatty acids) in plasma. The plasma SID directly alters blood pH and therefore independently changes acid–base status (17–20). The normal plasma SID of neonatal calves and adult cattle is approximately 40 mmol/L, and changes in plasma SID independently change plasma pH (20, 21). Two other factors, the plasma carbon dioxide tension (Pco_2), and the total plasma concentration of non-volatile buffers (Atot), also independently change plasma pH (22). Interestingly, administration of an intravenous fluid changes plasma SID, and thereby changes plasma pH, by an amount that depends on the solution SID and volume relative to plasma volume. Intravenous fluid

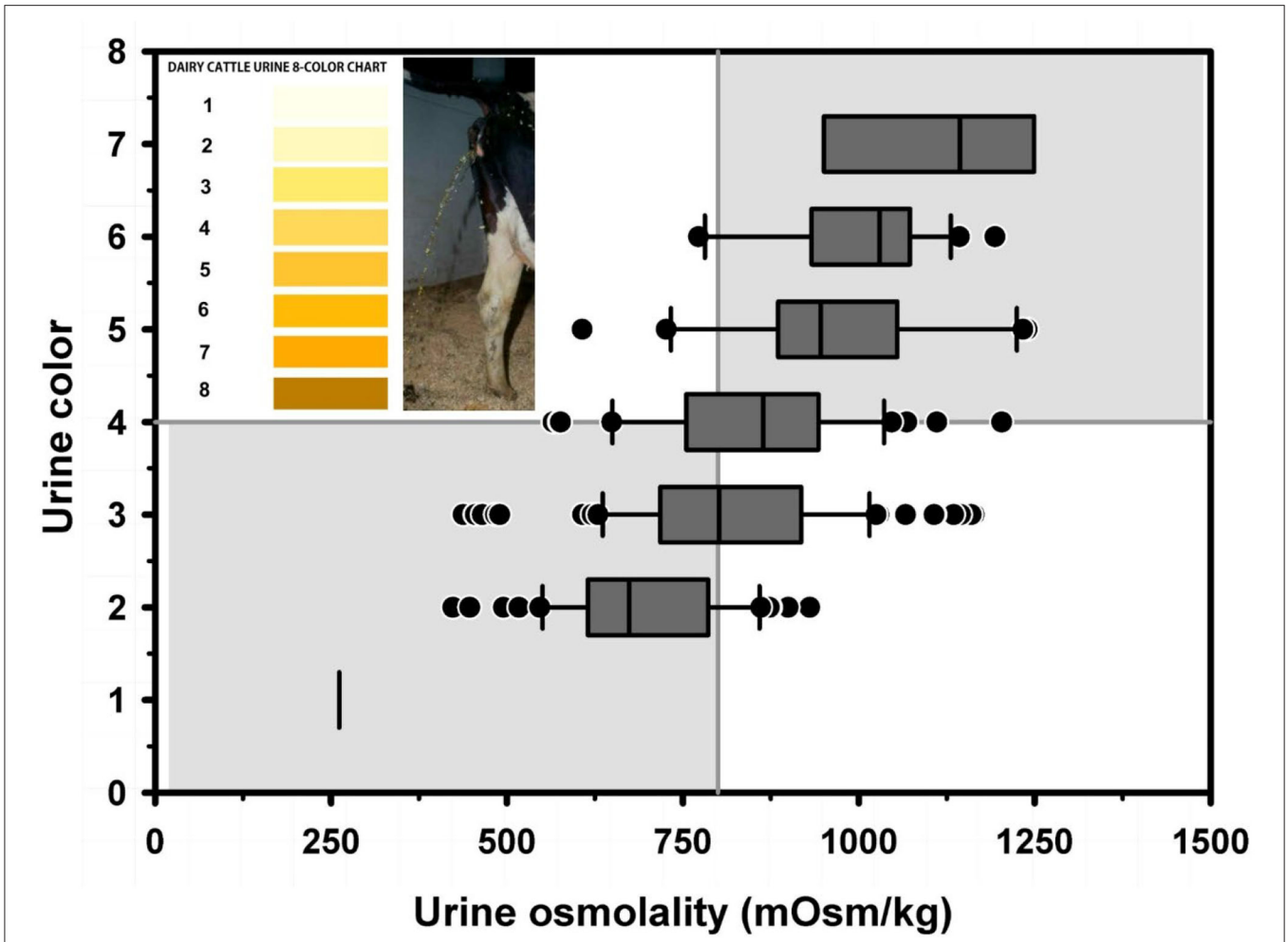

FIGURE 3 | Box and whiskers plot of the association between urine color (8 levels) and urine osmolality (UOsm; reference method) for 237 urine samples obtained periodically from 20 multiparous periparturient Holstein-Friesian cows. The solid gray vertical line indicates the recommended cut point for UOsm (≥800 mOsm/kg) for diagnosing dehydration. The solid gray horizontal line indicates the optimal cut point for color (≥4) identified by logistic regression for diagnosing dehydration. See **Figure 2** legend for additional information. Figure modified with permission from: Megahed et al. (5).

administration also dilutes the volume of distribution of plasma protein, the main non-volatile buffer in plasma, and this is accompanied by a decrease in plasma Atot and a direct decrease in plasma pH (23).

A physicochemical plot of plasma pH against the volume of solutions infused with differing SID provides an effective method for conveying the net alkalinizing or acidifying effect of intravenous crystalloid solution formulation on plasma pH [**Figure 5**; (19, 23)]. The approach was developed by Constable in 2004 (23), and a similar physicochemical approach was used in 2010 to plot Base Excess against the volume infused (24). The effect of infusing solutions of varying SID on plasma pH in calves can be calculated using Constable's 6-factor simplified strong ion equation (17, 18, 22) and applying experimentally determined values for Atot [0.343×(total protein in g/L)] and Ka (0.84×10^{-7}) of calf jugular venous plasma and mean values from healthy calves for plasma pH (7.419), Pco_2 (51 mm Hg), pK_1' (6.105), *S* [0.0307 (mmol/L)/mmHg], total protein concentration (58 g/L), and SID (46.7 mmol/L) (25, 26). **Figure 5** clearly indicates that 0.9% NaCl, 5% dextrose, or Ringer's solution decreases plasma pH in a dose dependent manner when infused intravenously, whereas intravenous administration of 1.3% sodium bicarbonate markedly increases plasma pH in a curvilinear manner. The overall effect of intravenous electrolyte solutions with an effective SID = 0 mmol/L, such as 0.9% NaCl or Ringer's solution, is a decrease in plasma pH because the strong ion acidosis causes a larger decrease in plasma pH than the independent effect of an increase in plasma pH due to concurrent non-volatile buffer ion alkalosis (21, 27). A surprising observation in calves is that lactated Ringer's solution, assuming L-lactate concentration is 14 or 28 mmol/L (28) and D-lactate is not metabolized, and acetated Ringer's solution, assuming gluconate is not metabolized, are predicted to produce a similar and very mild acidifying effect. This is because the intravenous

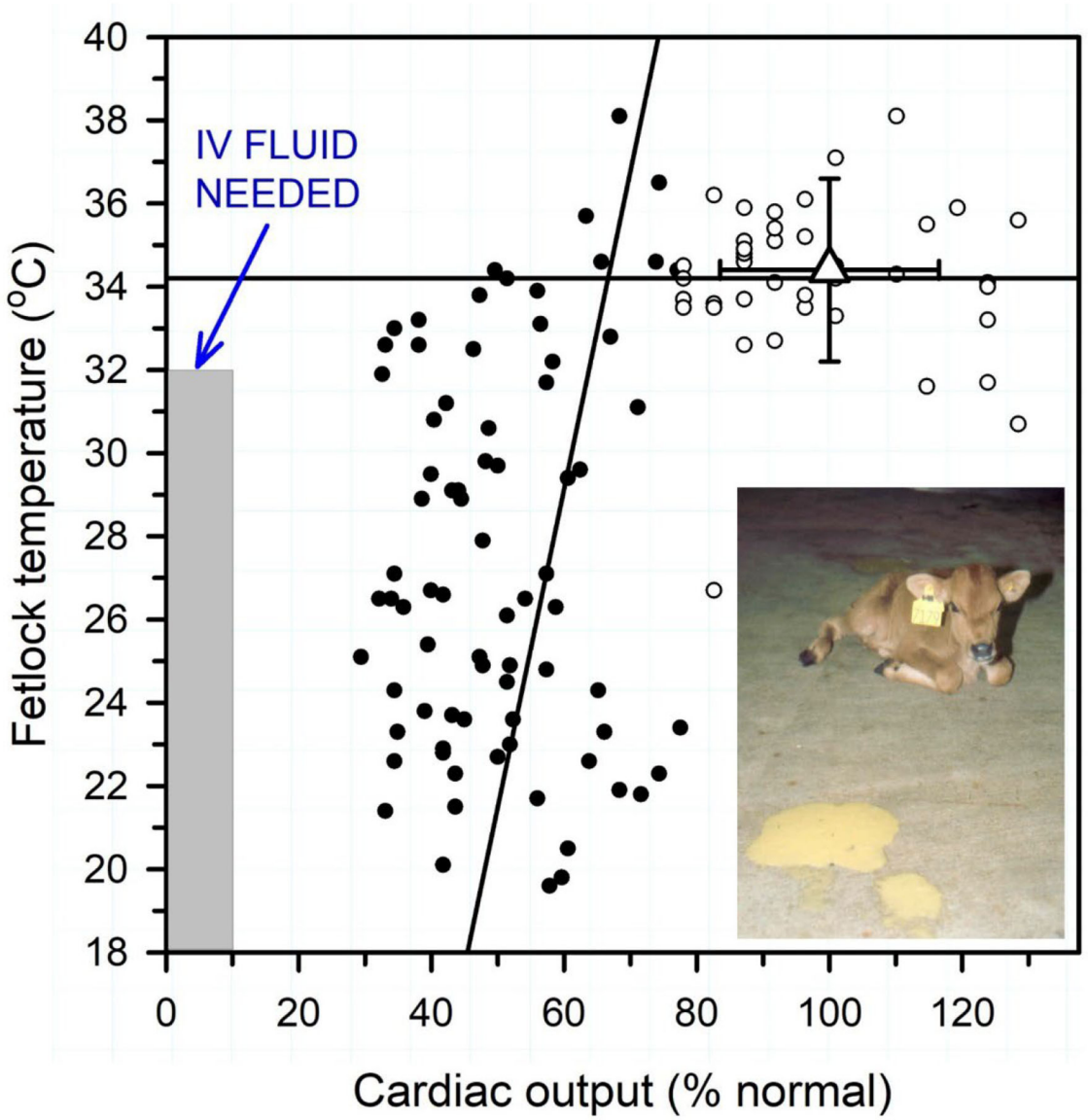

FIGURE 4 | Relationship between peripheral temperature (hind fetlock) and cardiac output (percent of normal) in diarrheic calves with varying degrees of dehydration housed in a thermoneutral environment. Normal mean cardiac output was 8.5 L/min or 218 ml/min/kg BW. Linear regression lines for cardiac output < 65% normal (solid circles) and >65% normal (open circles). Triangle with error bars indicates reference values for healthy neonatal calves. Note that fetlock temperature is positively correlated with cardiac output when cardiac output <65% of normal. Intravenous fluid therapy is recommended when hindlimb fetlock temperature is <32°C (< 90°F) when calves are housed in a thermoneutral environment. Figure modified with permission from Constable et al. (6).

administration of a crystalloid solution with an effective SID < 33 mmol/L will always be acidifying in healthy neonatal calves, whereas a crystalloid solution with an effective SID > 33 mmol/L will be alkalinizing (**Figure 5**), based on a plasma bicarbonate concentration of 33 mmol/L in healthy calves (26). Intravenous infusion of a solution with a SID of 40 mmol/L is mildly alkalinizing even though plasma SID remains constant at 40 mmol/L; this is because the addition of free water decreases plasma total protein and albumin concentrations, resulting in a mild increase in plasma pH. When a solution with a SID of 33 mmol/L is infused intravenously, the mild strong ion acidosis counterbalances the resultant mild non-volatile buffer ion alkalosis, with no net change in plasma pH. It should be noted that the decrease in plasma SID when 0.9% NaCl is administered depends upon the relative volume of the infused 0.9% NaCl solution to the initial extracellular space as well as the speed of 0.9% NaCl administration. Veterinarians should therefore be conversant with the SID of intravenous and oral fluid formulations as this plays an important role in optimizing fluid therapy.

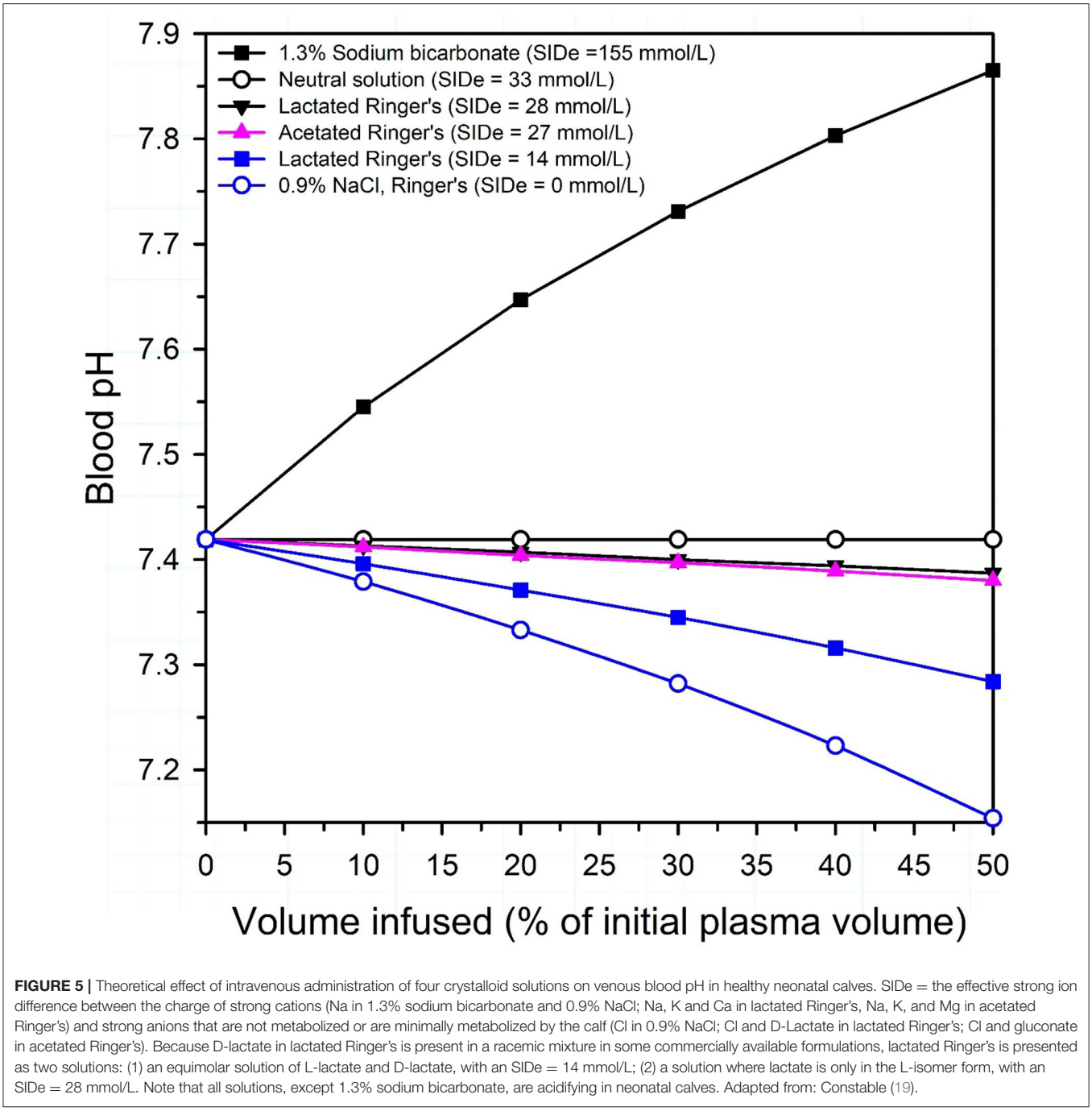

FIGURE 5 | Theoretical effect of intravenous administration of four crystalloid solutions on venous blood pH in healthy neonatal calves. SIDe = the effective strong ion difference between the charge of strong cations (Na in 1.3% sodium bicarbonate and 0.9% NaCl; Na, K and Ca in lactated Ringer's, Na, K, and Mg in acetated Ringer's) and strong anions that are not metabolized or are minimally metabolized by the calf (Cl in 0.9% NaCl; Cl and D-Lactate in lactated Ringer's; Cl and gluconate in acetated Ringer's). Because D-lactate in lactated Ringer's is present in a racemic mixture in some commercially available formulations, lactated Ringer's is presented as two solutions: (1) an equimolar solution of L-lactate and D-lactate, with an SIDe = 14 mmol/L; (2) a solution where lactate is only in the L-isomer form, with an SIDe = 28 mmol/L. Note that all solutions, except 1.3% sodium bicarbonate, are acidifying in neonatal calves. Adapted from: Constable (19).

The actual pH of commercially formulated intravenous fluids has no impact on its acidifying or alkalinizing potential; this statement does not hold in experimental conditions when strong acids or alkalis are infused, such as 300 mmol/L solutions of HCl or NaOH. The pH of commercially formulated solutions ranges from 5.5 to 8.0, and solution pH is determined primarily by the permeability of the polyvinyl chloride container to carbon dioxide (1). Diffusion of atmospheric CO_2 through the container wall into the solution will decrease solution pH. Autoclaving of polyvinyl chloride bags as part of the sterilization process can produce enough acetate and formate to also lower solution pH (1).

Isotonic, Hypertonic, and Hypotonic Intravenous Solutions

The tonicity of intravenous and oral electrolyte solutions is also an important clinical issue when treating critically ill neonatal calves and adult cattle, and an understanding of the difference between osmolarity and osmolality is required when selecting the optimal fluid therapy. **Osmolarity is calculated** from the

mass concentration of particles in a solution assuming complete dissociation of ionic compounds such as NaCl and is expressed as mOsm/L of solution (in the case of 0.9% NaCl the solution is water). **Osmolality is measured** in the laboratory and expressed in units of mOsm/kg of solvent to accurately reflect the number of dissolved particles per kilogram of solvent. In plasma the solvent is plasma water that includes suspended proteins such as albumin and globulin. The measured plasma osmolality in neonatal calves and adult cattle is approximately 285 mOsm/kg [range, 275 to 295 mOsm/kg; (29, 30)]. In general terms, plasma osmolality is actively defended when plasma osmolality >295 or <275 mOsm/kg by increasing water intake or promoting free water excretion by the kidneys, respectively. The correct physiologic term when describing the tonicity of plasma is osmolality. This is because plasma osmolality accounts for the presence of plasma proteins and other substances that are suspended but not dissolved in plasma water, which is the solvent.

It should be noted that in clinical applications, intravenous fluid solution osmolarity is usually calculated from the stated concentrations. For example, 0.9% NaCl solution has a NaCl concentration of 154 mmol/L and a calculated osmolarity of 308 mOsm/L (2 × 154) assuming complete dissociation of NaCl. However, some of the sodium ions (cation) and chloride ions (anion) remain electrostatically attracted to each other in biological solutions, depending in part on the solution tonicity, so that the net result is that some of the NaCl is not completely dissociated in solution. Instead, a 0.9% NaCl solution contains separate sodium ions, chloride ions, and sodium-chloride particles (31). Experimental studies have determined that a 154 mmol/L solution of NaCl is about 86% dissociated, equivalent to an osmotic coefficient φ {phi} of 0.93 for NaCl (32), so that placing 154 mmol of NaCl in 1 L of water results in 132 mmol of sodium ions, 132 mmol of chloride ions, and 22 mmol of sodium-chloride particles = 286 mmol of particles (1.86 × 154) per L of water. In other words, the theoretical osmolarity of a 154 mmol/L solution of NaCl is 286 mOsm/L, which approximates a calculated osmolality of 286 mOsm/kg that is similar to the measured osmolality of plasma water in healthy cattle. A 0.9% NaCl solution distributes in plasma water when administered intravenously and is therefore isotonic when administered to cattle. Intravenously administered Ringer's solution (osmolarity, 309 mOsm/L), 1.3% $NaHCO_3$ solution (osmolarity, 310 mOsm/L), and 5% dextrose solution (osmolarity, 278 mOsml/L) also distribute in plasma water and act as isotonic solutions when administered to cattle because they have calculated osmolalities of 287 mOsm/kg, 282 mOsm/kg, and 279 mOsm/kg, respectively. These osmolalities were calculated assuming that φ approximates 0.93 for Ringer's solution in plasma water, 0.91 for 1.3% sodium bicarbonate in plasma water (33), and 1.005 for dextrose in plasma water (34). It should be noted that a 5% dextrose solution can be obtained by adding 50 g of anhydrous dextrose with a molecular weight of 180 g to 1 L of water, or by adding 55 g of dextrose monohydrate, which is the most commonly used compound with a molecular weight of 198 g to 1 L of water.

On the above basis and in approximate terms, intravenous solutions administered to cattle can be defined as isotonic (275–295 mOsm/kg), hypotonic (<275 mOsm/kg), or hypertonic (>295 mOsm/kg) when osmolality is calculated from solution concentrations using the appropriate osmotic coefficient (9). It is not widely appreciated that some commonly used crystalloid solutions are hypotonic in calves and adult cattle when this classification system is used. For example, a buffered formulation of acetated Ringer's solution (Plasma-Lyte 148; calculated osmolarity, 295 mOsm/L; measured osmolality, 271 mOsm/kg) is mildly hypotonic, whereas lactated Ringer's solution (calculated osmolarity, 273 mOsm/L; measured osmolality, 256 mOsm/kg) is moderately hypotonic (1, 35, 36). Bovine erythrocytes are resistant to increases in plasma osmolality but susceptible to mild decreases in osmolality; intravenous fluids administered to cattle should ideally be isotonic or hypertonic because of the potential for hypotonic-induced hemolysis when large volumes of hypotonic solutions are rapidly administered (9). Nevertheless, the tonicity of lactated Ringer's solution is not low enough to raise clinical concerns of intravascular hemolysis in calves and adult cattle, although the additional free water is of theoretical concern when lactated Ringer's solution is rapidly administered in high volumes to endotoxemic animals.

In summary, lactated Ringer's solution and acetated Ringer's solution are polyionic crystalloid solutions that appear to be safe in neonatal calves and adult cattle. These two solutions have been widely used for treating moderate dehydration, electrolyte imbalances, and acidemia or alkalemia (9, 37). Unfortunately, lactated Ringer's solution and acetated Ringer's solution are not optimally formulated for ruminants and they are not usually adequate for treating neonatal calves or adult cattle with severe acidemia or alkalemia, hyponatremia, hypokalemia or hypochloremia.

Distribution Space of Intravenously Administered Electrolytes

A critical factor in determining the amount of alkalinizing agent to provide to acidemic calves and adult cattle is an accurate knowledge of the total deficit. The total deficit of a plasma electrolyte in millimoles (mmol) is calculated as the deficit of the electrolyte in mmol per liter (Δmmol/L) multiplied by the distribution space for the electrolyte. The distribution space for sodium, chloride and bicarbonate is the extracellular fluid volume, which approximates 30% of BW in euhydrated adult cattle (38) and 44% in euhydrated neonatal calves (15). The total millimole deficit of sodium, chloride and bicarbonate for adult cattle or neonatal calves can be calculated as: deficit = (Δmmol/L) × (body weight in kg) × (0.30 or 0.44), respectively (7). Interestingly, the apparent bicarbonate space (apparent distribution volume for administered bicarbonate) in acidemic neonatal calves with diarrhea often appears to be greater than 0.44, and has been calculated to be 0.65 in 36 neonatal calves with naturally acquired diarrhea (39), 0.63 and 0.84 in 73 dehydrated diarrheic calves (40) and 0.73 and 0.78 in 11 healthy neonatal calves (41).

A notable clinical observation in neonatal calves, adult cattle, humans, and dogs is that the apparent bicarbonate space (ABS)

is higher when the initial plasma bicarbonate concentration ($cHCO_3$) is low. Based on a recent study in dehydrated calves with diarrhea (42), a rule of thumb would be to use an ABS value of 0.53 for dehydrated calves with diarrhea; however, when the results of jugular venous blood gas analysis are available, the apparent bicarbonate space (ABS) can be calculated from either the calculated value for venous $cHCO_3$ or the measured value for Pco_2, such that: $ABS = 0.41 + 1.06/cHCO_3$ and $ABS = 0.87 - 0.0082 \times Pco_2$ (42). Adult cattle are likely to require a similar adjustment of the ABS value for the initial plasma $cHCO_3$.

INTRAVENOUS FLUID THERAPY IN NEONATAL CALVES WITH DIARRHEA

The major goals of intravenous fluid therapy in diarrheic calves are to: (a) expand the extracellular fluid volume and thereby restore venous return; (b) correct acidemia in calves with a jugular venous blood pH < 7.20 due to metabolic acidosis; (c) restore the suckle reflex and correct mental depression; (d) correct electrolyte abnormalities; (e) correct the energy deficit; and (f) facilitate repair of damaged intestinal epithelium (9, 10), although the latter goal is more appropriately addressed by oral administration of fresh cow's milk or an oral electrolyte solution (OES). Intravenous fluid administration should be monitored and intermittently reassessed (1, 9).

Studies based on the analyses of large datasets of diarrheic calves have shown that hyponatremia and unmeasured anions such as D-lactate are the most important contributors to acidemia in neonatal diarrheic calves (25, 43). Acidemia is also more common in dehydrated calves due to the hydration reduced decrease in glomerular filtration rate and therefore decreased ability to excrete a systemic acid load (44, 45). The preferred intravenous alkalinizing agent in neonatal calves with moderate acidemia, defined as blood pH < 7.20, is sodium bicarbonate. Metabolizable sodium salts of acetate and L-lactate result in a delayed increase in plasma bicarbonate, with L-lactate metabolism being slower than acetate metabolism (41). Gluconate and D-lactate are very slowly metabolized in neonatal calves and should not be administered as an alkalinizing agent (41, 46).

An optimized decision tree has been developed for treating neonatal calves with dehydration and/or strong ion (metabolic) acidosis due to diarrhea [**Figure 6**; (47)]. The decision tree is based on ability to stand, hydration status (degree of enophthalmos), suckling strength, and presence or absence of a palpebral reflex. The need for oral fluids or intravenous administration of 250, 500, or 750 mmol of sodium bicarbonate, preferably as an isotonic solution with supplemental glucose added when indicated as part of the initial treatment, is identified by the decision tree (47). The decision tree also allows for short-term infusions of small-volume hypertonic $NaHCO_3$ solutions with subsequent oral rehydration for treatment of calves with clinical signs of metabolic acidosis but no or minimal dehydration. The addition of 20 ml of 50% glucose solution to every liter of the initial intravenous fluid solution (providing 10 g glucose/L of solution) is beneficial on the first day of treatment of depressed diarrheic calves as hypoglycemia is common and associated with mortality (48, 49). However, subsequent glucose supplementation of intravenous solutions is not recommended as sustained intravenous glucose administration (10 g or 40 g glucose/L of solution) is associated with decreased voluntary milk intake (50).

Isotonic and Hypertonic Sodium Bicarbonate Solutions

Isotonic sodium bicarbonate (1.3% $NaHCO_3$ solution), an alkalinizing isotonic crystalloid solution, is the preferred treatment of neonatal calves with diarrhea, dehydration and moderate to severe acidemia. Isotonic sodium bicarbonate solution should be administered in calves with blood pH < 7.20 as a result of strong ion acidosis (51). Sodium bicarbonate exerts its alkalinizing action by buffering hydrogen ions, such that:

$$HCO_3^- + H^+ \rightleftharpoons CO_2 + H_2O,$$

and increases plasma SID, as the effective SID of isotonic sodium bicarbonate solution is 155 mmol/L (23). Sodium bicarbonate is preferred to sodium L-lactate and sodium acetate solutions for treating neonatal calves with diarrhea and moderate to marked metabolic acidosis because it provides an immediate source of bicarbonate (39). Because diarrheic calves are usually hyponatremic, a mildly hypertonic 1.4% $NaHCO_3$ solution (calculated osmolality, 304 mOsm/kg, Na concentration = 167 mmol/L) is preferred by some clinicians over a 1.3% $NaHCO_3$ solution [calculated osmolality, 282 mOsm/kg; Na concentration = 155 mmol/L; 52].

Intravenous sodium bicarbonate solutions should not be administered to critically ill calves with respiratory disease on theoretical grounds because the additional CO_2 generated may exacerbate hypercapnia and respiratory acidosis and decrease cerebrospinal fluid pH. A reasonable clinical recommendation is therefore to avoid administering intravenous hypertonic sodium bicarbonate solutions to calves with clinical signs of respiratory distress, such as marked thoracic excursions and abnormal auscultation or ultrasonographic findings. Attention should also be paid to early signs of hypercapnia such as muscle tremors and fasciculation while infusing hypertonic sodium bicarbonate. Nevertheless, studies in critically ill neonatal calves have not identified a clinically important effect of sodium bicarbonate infusion on increasing arterial Pco_2 and further decreasing blood pH. The rapid administration of large volumes of sodium bicarbonate produces systemic alkalinization that may be accompanied by paradoxic cerebrospinal fluid (CSF) acidosis and adverse neurologic sequelae (52, 53). It should be noted that paradoxic CSF acidosis has only been reported in animals with controlled ventilation (7), and does not occur when sodium bicarbonate is administered to animals that control their own ventilation because any decrease in arterial blood pH due to an increase in arterial Pco_2 results in a reflex increase in minute volume to combat the hypercapnia and respiratory acidosis (52).

Hypertonic sodium bicarbonate solutions are clinically effective for treating acidosis and hyperkalemia in neonatal calves with acute diarrhea, D-lactic acidosis, or mixed respiratory

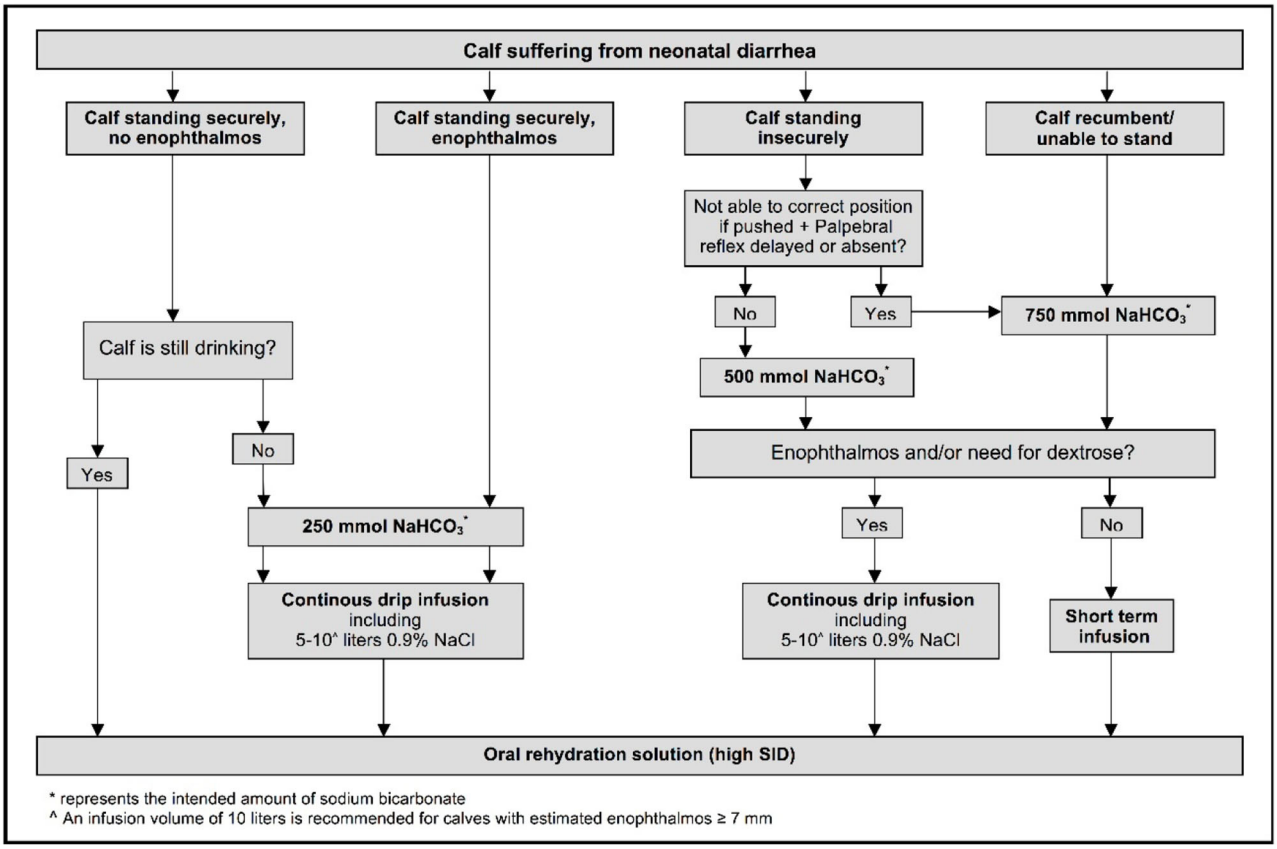

FIGURE 6 | Decision tree for treating neonatal calves with diarrhea. The ability to stand is evaluated by lifting recumbent calves. Enophthalmos reflects a visible gap of 3–4 mm between the corneal surface of the eye and normal position of the lower eyelid. Reprinted with permission from: Trefz et al. (47).

and strong ion (metabolic) acidosis (54–57). An 8.4% solution of sodium bicarbonate (2,000 mOsm/L) provides rapid alkalinization. An osmolarity of 2,000 mOsm/L is preferred because it provides 1 mmol of HCO_3/ml of solution that permits simple calculation of the administered fluid volume. An 8.4% solution of sodium bicarbonate should not be administered faster than 1 ml/kg BW per minute when a total dose of bicarbonate (5 ml/kg BW) over 5 min in infused. This treatment regimen in normovolumic calves with experimentally induced mixed respiratory and metabolic acidosis caused a rapid increase in blood pH and improved cardiovascular status without inducing paradoxical cerebrospinal fluid acidosis (52). A subsequent study in calves with experimentally induced acidemia and hyperchloremic acidosis administered isotonic sodium bicarbonate solution over 4 h also failed to observe paradoxical cerebrospinal fluid acidosis (53). A 2008 study in dehydrated calves with naturally acquired diarrhea compared the resuscitative response of IV hypertonic sodium bicarbonate solution (8.4%, 10 ml/kg BW over 8 min) to IV hypertonic sodium chloride solution (5.9%, 5 ml/kg BW over 4 min); however, it should be noted that the hypertonic sodium chloride group received half the overall sodium load to that administered to the hypertonic sodium bicarbonate group. Both groups of calves also received 3 L of an OES 5 min after IV administration. The results of the study indicated that hypertonic sodium bicarbonate solution was more effective than hypertonic saline solution in correcting moderate acidemia and metabolic acidosis (56). Finally, a 2010 study of neonatal dehydrated calves with diarrhea compared the rapid IV administration of hypertonic (8.4%) and isotonic (1.3%) solutions of sodium bicarbonate administered at different volumes but similar sodium loads. The results of this study indicated that isotonic sodium bicarbonate solution was superior in rehydrating the calf because it contained more free water, whereas the rapid administration of the hypertonic solution was faster at correcting the acidemia and metabolic acidosis (54).

A major challenge with administering sodium bicarbonate solutions to dehydrated calves and adult cattle is the cost and availability of commercial products. This is because a high solution Pco_2 tension must be maintained in solution to prevent dissociation of HCO_3^- to CO_3^{2-} and the precipitation of calcium carbonate within the solution. Carbon dioxide impermeable containers, such as glass, are needed to prevent carbon dioxide from leaving solutions of sodium bicarbonate. Commercially formulated bicarbonate solutions are therefore available only in glass containers that rarely exceed 1 L in

volume. Bicarbonated Ringer's solution was formulated in Japan in 2005 in 500 mL plastic bottles and contained bicarbonate (25 mmol/L) and citrate (5 mmol/L) to prevent formation of calcium and magnesium precipitates (58), but this solution is now unavailable. Cattle veterinarians currently formulate sodium bicarbonate solutions for immediate use, often using 500 mL glass bottles of 5% sodium bicarbonate or 50–100 ml glass bottles of 8.4% sodium bicarbonate as a basis for solution formulation for administration to neonatal calves.

Isotonic and Hypertonic Sodium Chloride Solutions

Isotonic sodium chloride (0.9% NaCl) is an acidifying isotonic crystalloid solution that has several shortcomings for treating neonatal calves with diarrhea and dehydration. Although isotonic and containing a sodium concentration of 154 mmol/L which is beneficial in calves with diarrhea as they are frequently hyponatremic (25), the effective SID of the solution is 0 mmol/L and consequently the solution is acidifying when administered intravenously (**Figure 5**). Moreover, 0.9% NaCl solution does not contain potassium, and neonatal calves with diarrhea have been thought for many years to be potassium deficient (59), despite some calves having hyperkalemia (9, 45, 60, 61). The assumption that diarrheic calves have whole body depletion of potassium has been recently challenged in a study of calves with acute diarrhea and marked dehydration and acidemia, in that diarrheic calves had similar skeletal muscle potassium concentrations to healthy calves (62). Possibly whole-body potassium deficiency only occurs in calves with chronic diarrhea, or does not occur at all.

Small volumes (4–5 ml/kg BW) of hypertonic NaCl solutions (7.0 to 7.5% NaCl) have been extensively investigated for treating hypovolemic shock in domestic animals and humans. The results of physiologically focused studies indicate that hypertonic saline increases plasma volume by osmotically driving free water to move from the intracellular space to the extracellular space where the translocated free water is retained by the additional sodium load. This increases the cardiac output despite a transient decrease in cardiac contractility, increases mean circulatory filling pressure, systemic oxygen delivery, and mean arterial blood pressure, while decreasing total peripheral vascular resistance and pulmonary vascular resistance (63, 64). The resultant increase in glomerular filtration rate restores urine output and acid–base balance returns toward normal due to improved organ perfusion and renal clearance of protons (65).

The most commonly used hypertonic saline formulation for the rapid resuscitation of animals with hypovolemia is 7.2% NaCl (2,460 mOsm/L). Hypertonic saline should be intravenously administered at 4–5 ml/kg BW over 4–5 min, equivalent to 1 ml/kg BW per minute. Faster administration rates directly cause vasodilation and decreased cardiac contractility, resulting in hemodynamic collapse (63, 64). Similar to the intravenous administration of high-volume 0.9% NaCl solution that has an effective SID = 0 mmol/L, small-volume 7.2% NaCl solution induces a mild strong ion acidosis and transient decrease in pH of up to 0.08 pH units that rapidly dissipates with time and is thought to not be clinically important (65).

Intravenous hypertonic saline (7.2–7.5% NaCl) administered through an 18 g needle at 4–5 ml/kg BW over 4–5 min, alone or accompanied by the colloid dextran-70, has been used to successfully resuscitate dehydrated calves with diarrhea [**Figure 7**; (13, 51, 57, 66–68)]. Dextran accompanied hypertonic saline in the initial studies in calves because it produces sustained plasma volume expansion in other shock models (13, 66, 67); however, subsequent studies have indicated that a beneficial response can be obtained without dextran (8, 51, 68, 69). The clinical response to treatment is optimized if calves receive 2–3 L of an isotonic OES by esophageal intubation immediately before hypertonic saline is administered (7, 65). The fastest rate of resuscitation is produced by combined administration of intravenous hypertonic saline and an OES, based on the speed of increase in plasma volume, stroke volume, and cardiac output (13, 51, 66), and the rate of resuscitation with the combined treatment is faster than that provided by lactated Ringers solution administered at 80 mL/kg during the first hour of infusion [(13, 51); **Figure 8**]. Consequently, when treating dehydrated diarrheic calves that are not markedly acidemic (i.e., blood pH anticipated to be >7.20), the rapid infusion of small volumes of hypertonic saline is preferred over the infusion of large volumes of lactated Ringer's solution. Moreover, hypertonic saline administration results in greater retention of the administered sodium and sustained resuscitation, whereas lactated Ringers solution or 0.9% NaCl solution increase urinary sodium and free water loss (13, 66, 68).

Lactated Ringer's Solution

Lactated Ringer's solution is a moderately hypotonic (256 mOsm/kg) balanced, polyionic, crystalloid solution containing physiological concentrations of K^+, Ca^{2+}, and Cl^-, and concentrations of Na^+, L-, and D-lactate ($CH_3CH(OH)COO^-$) that differ from that of cattle plasma. The solution is commonly administered to calves with mild to moderate dehydration that can stand but have a poor or no suckle response (8, 9, 13, 37). Lactated Ringer's solution is widely regarded as mildly alkalinizing because the strong anion L-lactate can be removed from plasma via gluconeogenesis in the cytosol to produce glucose, an uncharged molecule, while consuming two protons (41), such that:

$$2CH_3CH(OH)COO^- + 2H^+ \longleftrightarrow C_6H_{12}O_6$$

A variable amount of L-lactate is converted to pyruvate by lactate dehydrogenase in the cytosol, thereby consuming a proton, and then oxidized in mitochondria through the citric acid pathway to produce carbon dioxide and water (41); the final metabolic products are not strong anions and consequently the plasma SID and blood pH increase. The overall metabolic fate of L-lactate via oxidation can be summarized as:

$$2CH_3CH(OH)COO^- + 2H^+ + 6O_2 \rightarrow 6CO_2 + 6H_2O.$$

Finally, a very small amount of L-lactate in plasma is excreted in the urine, particularly when plasma L-lactate concentrations are

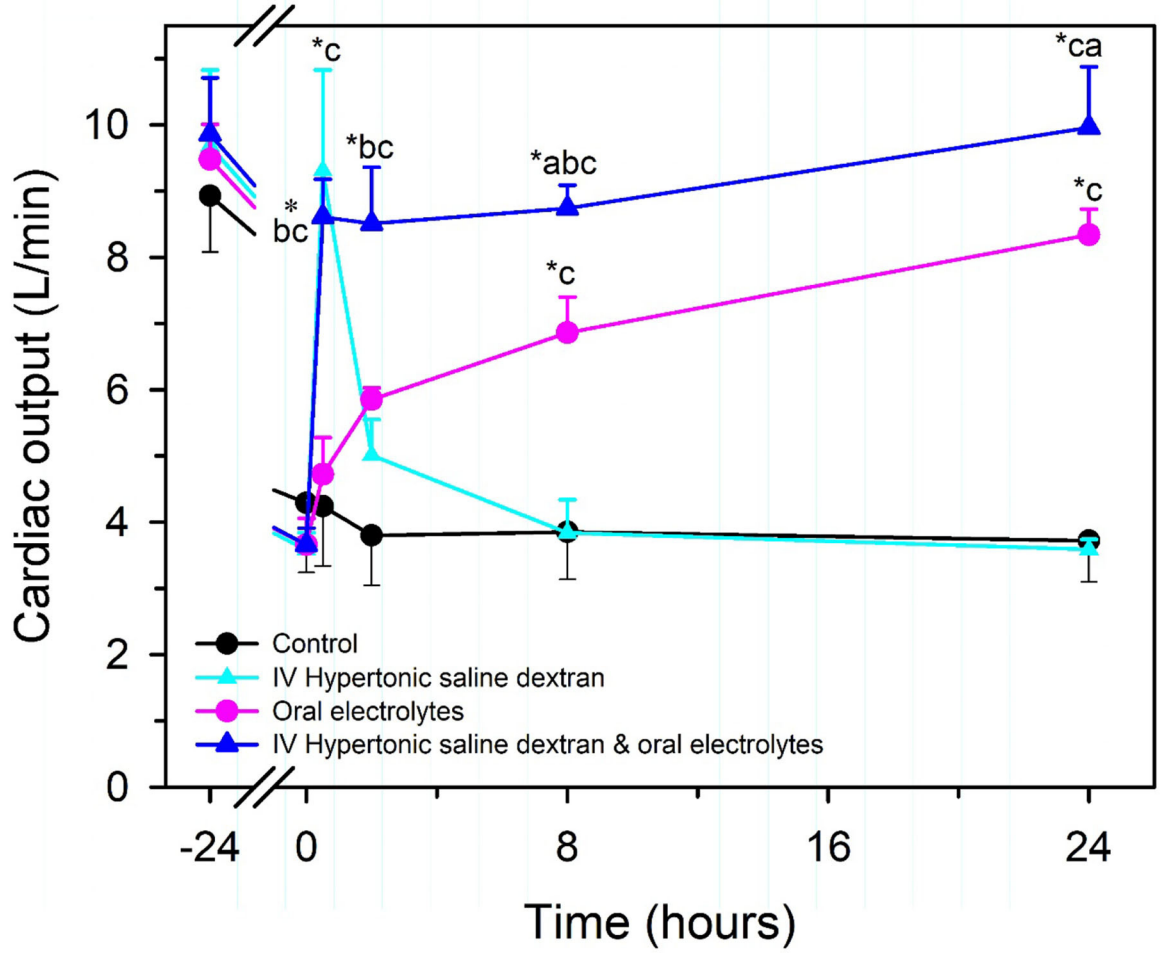

FIGURE 7 | Cardiac output in healthy neonatal calves (time = −24 h) and after experimentally induced diarrhea and dehydration (time = 0 h). Calves were then randomly assigned to no treatment (Control; black circles, $n = 4$) or treatment with an intravenous hypertonic saline-dextran (HSD) solution (2,400 mOsm/L NaCl in 6% dextran-70 at 4 ml/kg BW once over 4 min; cyan triangles, $n = 4$), an isotonic alkalinizing oral electrolyte solution (55 ml/kg BW every 8 h for three treatments; pink circles, $n = 4$); or a combination of intravenous HSD and oral treatments (blue triangles, $n = 4$). $^{*}P < 0.05$, compared with $t = 0$ value; $^{a}P < 0.05$ compared with hypertonic saline dextran group; $^{b}P < 0.05$ compared with oral electrolyte solution; and $^{c}P < 0.05$, compared with the untreated control group. Adapted, with permission, from: Constable et al. (66).

high, and this also represents a loss of a plasma strong anion and subsequent increase in plasma SID.

Lactated Ringer's solution is typically a racemic mixture of L-lactate and D-lactate that historically contained approximately equivalent concentrations of L-lactate and D-lactate isomers. The L-lactate isomer predominates in most currently available commercial products (28). L-lactate is rapidly metabolized to bicarbonate in mammals, including neonatal calves; however, mammals have minimal D-lactate dehydrogenase. This results in slowed clearance of D-lactate that occurs primarily by excretion through the urinary system (41). Racemic DL-lactate solutions therefore have an effective SID less than the calculated value of 28 mmol/L for lactated Ringer's solution. The net result is that lactated Ringer's solution has an effective SID of 14–28 mmol/L and is neutral to slightly acidifying from a physicochemical perspective when administered to healthy calves with normal acid–base balance [**Figure 5**; (70, 71)] because the mean plasma bicarbonate concentration of healthy calves is 33 mmol/L (26). However, it should be recognized that if the lactated Ringer's formulation contains only the L-isomer, lactated Ringer's solution will be alkalinizing whenever the plasma bicarbonate concentration is <33 mmol/L, which is frequently the case in diarrheic calves (25, 43, 49). Severely dehydrated calves can have increased blood L-lactate concentrations and a 50% decrease in the rate of L-lactate metabolism (72). The latter finding suggests that it may be clinically irrational to add additional L-lactate to hyperlactatemic neonatal calves.

Increasing the L-lactate concentration of lactated Ringer's solution should produce a mild to moderate alkalinizing effect, and in healthy calves the addition of L-lactate at 56 or 84 mmol/L

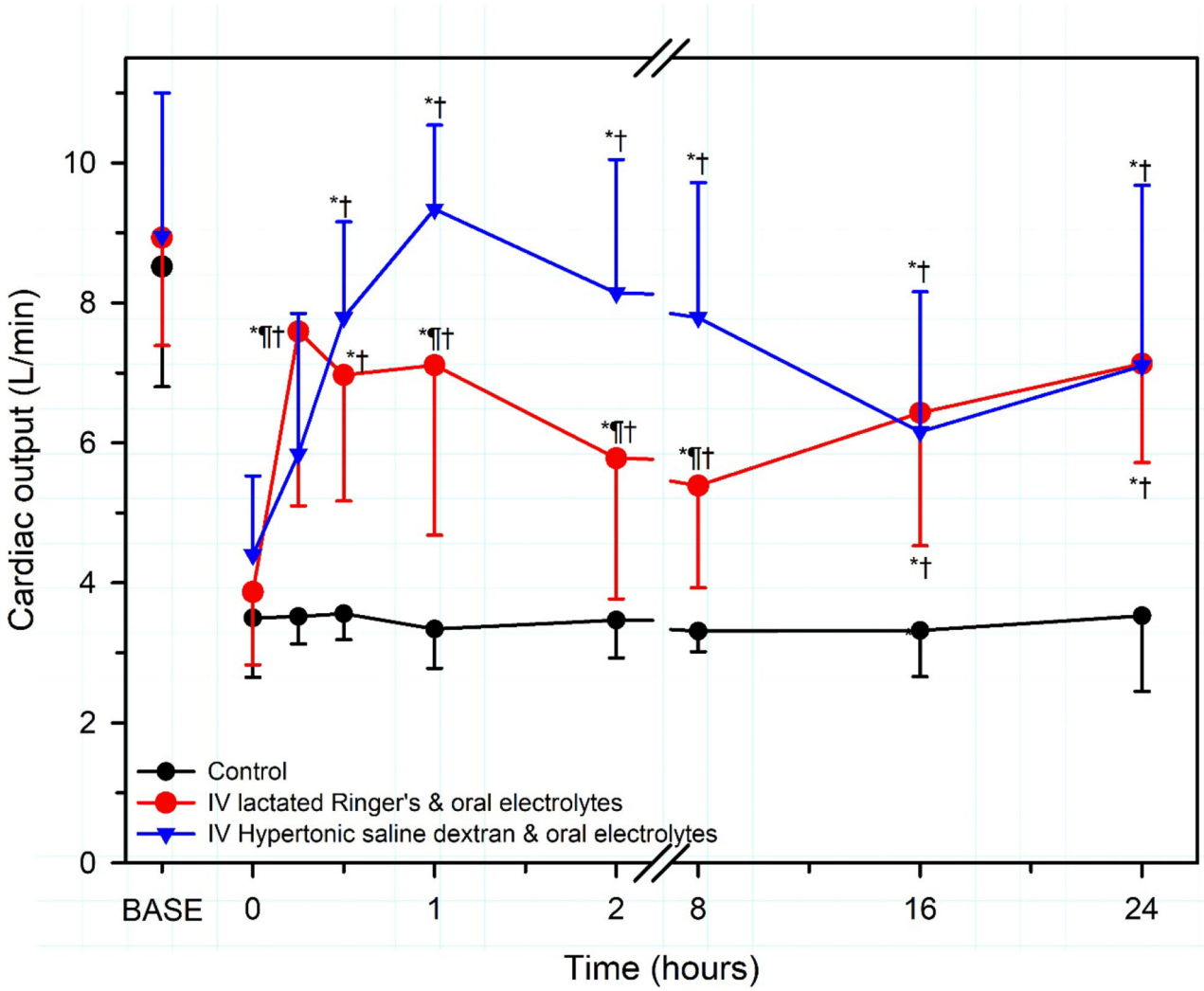

FIGURE 8 | Cardiac output in severely dehydrated diarrheic calves treated with no fluid (Control, black circles; $n = 5$); intravenous lactated Ringer's solution (80 ml/kg BW for 1 h then 4 ml/kg BW for 7 h) and an oral electrolyte solution (OES; 40 ml/kg BW at 8 and 16 h; red circles, $n = 5$); or intravenous hypertonic saline-dextran solution (HSD, 2,400 mOsm/L NaCl in 6% dextran-70 at 4 ml/kg BW once over 4 min) combined with an OES (60 ml/kg BW every 8 h for three treatments, blue triangles, $n = 5$). Base refers to baseline, the time before induction of diarrhea and dehydration. *significantly different from time = 0 h; † significantly different from control group at the same time; ¶significantly different from the lactated Ringer's group at the same time. Revised, with permission, from: Walker et al. (13).

to a 0.9% NaCl solution provided a similar alkalinizing effect to that provided by adding bicarbonate at 56 or 84 mmol/L (71). It is likely that the clinical effectiveness of lactated Ringer's solution in neonatal calves can be improved by increasing the L-lactate concentration, eliminating the D-lactate isomer, and increasing the Na concentration to 140 mmol/L.

Acetated Ringer's Solution

Acetated Ringer's solution is a slightly hypotonic (271 mOsm/kg) balanced, polyionic crystalloid solution containing physiological concentrations of Na^+, K^+, Mg^{2+}, and Cl^- and concentrations of acetate (CH_3COO^-) and gluconate ($CH_2(OH)\{CH(OH)\}_4COO^-$) that differ markedly from that of cattle plasma. Acetated Ringer's solution is widely regarded as a mildly alkalinizing solution because acetate is metabolized to carbon dioxide and water while consuming a proton (41), such that:

$$CH_3COO^- + H^+ + O_2 \rightarrow 2CO_2 + 2H_2O.$$

Acetated Ringer's solution is alkalinizing because acetate, a metabolizable strong anion, increases plasma SID when metabolized. It is not widely appreciated that the gluconate in acetated Ringer's is problematic because calves (and presumably all mammals) do not metabolize, or very slowly metabolize, gluconate (41, 46); consequently, gluconate acts as a strong anion when administered intravenously, counteracting any potential alkalinizing effects of acetate (46). The net result is that acetated Ringer's solution is neutral to slightly acidifying from a

physicochemical perspective (**Figure 5**) when administered at 20 ml/kg BW per hour to diarrheic calves (73). Contrary to popular belief, acetated Ringers solution is theoretically slightly acidifying in calves because its effective SID of 28 mmol/L is less than the mean plasma bicarbonate concentration for calves [33 mmol/L; (26)]. However, it should be recognized that acetated Ringer's solution will be alkalinizing whenever the plasma bicarbonate concentration is much lower than 33 mmol/L, which is frequently the case in diarrheic calves (25, 43, 49), because metabolism of acetate consumes a proton which is equivalent to generating a bicarbonate molecule.

Acetated Ringer's solution is commercially available in three formulations in North America, Plasma-Lyte A, Plasma-Lyte 148, and Normosol-R. All three have similar formulations except Plasma-Lyte A and Normosol-R have a solution pH of 7.4, compared to Plasma-Lyte 148 that has a solution pH of 6.0 (1); however, the solution pH difference is not clinically significant. Acetated Ringer's solution has the clinical advantage over lactated Ringer's solution in that its sodium concentration (140 mmol/L) is approximately the same as that of neonatal calves. The sodium concentration in lactated Ringer's solution (130 mmol/L) is appreciably lower. An additional advantage of Acetated Ringer's solution is that the rate of acetate metabolism to bicarbonate is faster than that of L-lactate (39, 41, 70). The main disadvantage of acetated Ringer's solution is that the solution is vasodilatory due to the inclusion of acetate (74–76), resulting in mild decreases in mean arterial blood pressure during infusion. This reduction may be clinically important in critically ill neonatal calves. It is likely that the clinical effectiveness of acetated Ringer's solution in neonatal calves can be improved by eliminating gluconate from the formulation. Studies that compare the ability of equal sodium and strong anion loads of acetated Ringer's solution (without gluconate) and lactated Ringer's solution (without the D-lactate isomer) to alkalinize and expand the plasma volume in neonatal calves with diarrhea are indicated.

Other Intravenous Solutions

Many intravenous solutions for fluid therapy of calves with diarrhea have been proposed and a consensus recommendation for home-formulated intravenous solutions are that they should contain approximately 150 mmol/L of sodium, 5 mmol/L of potassium and at least 50 mmol/L of bicarbonate or bicarbonate precursors such as L-lactate or acetate (9). Other intravenous solutions (Darrow's solution, McSherry's balanced electrolyte solution, Tromethamine, and Carbicarb) have been administered to neonatal calves with diarrhea. Some of these solutions have theoretical advantages over existing solutions, but these solutions are not currently used because commercially available formulations are not available.

Darrow's solution is an isotonic polyionic solution that was formulated in 1946 for administration to dehydrated human infants (77). Darrow's solution has been administered to calves but when compared to acetated Ringer's solution, Darrow's solution has a low sodium, high potassium and high lactate concentrations and does not contain magnesium. McSherry's balanced electrolyte solution is an isotonic polyionic solution that was formulated in 1954 for parenteral administration to dehydrated calves with diarrhea (78). This appears to be an excellent parenteral fluid that deserves research investigation (7).

Tromethamine is an organic amine (THAM, *t*ris-*h*ydroxymethyl *a*mino*m*ethane, $(CH_2OH)_3C\text{-}NH_2$) formulated as an isotonic solution (300 mmol/L) that is a safe and effective buffer in biological fluids. After intravenous administration to mammals, approximately 70% of the uncharged tromethamine compound is immediately protonated in plasma at physiologic pH to the strong cation $(CH_2OH)_3C\text{-}NH_3^+$ (79), with the net buffer equation being:

$$(CH_2OH)_3C\text{-}NH_2 + H^+ \rightleftharpoons (CH_2OH)_3C\text{-}NH_3^+.$$

The unprotonated form of tromethamine can cross cell membranes and theoretically buffer the intracellular compartment. Tromethamime should be administered in conjunction with electrolytes as its administration without additional electrolytes leads to hyponatremia (79). Tromethamine does not currently offer any documented advantages to the administration of an isotonic sodium bicarbonate solution in acidemic neonatal calves, and consequently its administration is not recommended.

Carbicarb® is an isotonic buffer (300 mOsm/L) that contains equimolar amounts of disodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) that completely dissociate in plasma; however, carbonate generates HCO_3 when buffering acidemic blood, and the generated HCO_3 can also buffer the proton, such that:

$$HCO_3^- + CO_3^{2-} + 3H^+ + 3Na^+ \rightleftharpoons 2CO_2 + 2H_2O + 3Na^+$$

Carbicarb® was anticipated to decrease the magnitude and occurrence of hypercapnia when administered to animals with mixed metabolic and respiratory acidosis (80, 81). Potential clinical advantages of Carbicarb® are only apparent in animals with limited ventilatory ability or controlled ventilation (7). Carbicarb® has been administered intravenously to neonatal calves with diarrhea (80) and newborn calves with metabolic acidosis when rapid alkalinization of neonatal calves with diarrhea is required (81). In these studies, Carbicarb® did not provide a clinically relevant advantage over isotonic sodium bicarbonate administration and its use is therefore not currently recommended.

INTRAVENOUS FLUID THERAPY IN CALVES WITH CLINICAL COCCIDIOSIS

Most fluid therapy studies have been conducted on neonatal calves that are < 21 days of age because of the high incidence of diarrhea during the first three weeks of life. Twenty-one days of age is also an appropriate physiologic cut-point for categorization, as calves that are conventionally raised (non-veal) are regarded physiologically as a monogastric from birth to 21 days of age, in a transition period from 3 to 8 weeks of age, and as a ruminant beyond 8 weeks of age. These age categories are associated with different forestomach flora and plasma concentrations of glucose, B-OH butyrate, and short

chain volatile fatty acids, consistent with the change from the primary source of energy transitioning from milk to forage.

Coccidiosis, and to a lesser extent giardiasis, are common causes of large intestinal diarrhea in calves from 28 days to 6 months of age. Only a few peer-reviewed studies have been published that describe the clinicopathological changes in calves with clinical coccidiosis (82, 83). Clinical experience indicates that calves with clinical coccidiosis are rarely acutely dehydrated because they increase their water intake in response to increased fecal water loss; however, hyponatremia can be much more severe in calves with coccidiosis than in neonatal calves with diarrhea due to cryptosporidia, rotavirus, coronavirus, and enterotoxigenic *E. coli*. Another important difference in bovine coccidiosis is that hyponatremia is usually accompanied by hypochloremia; this is because similar percent reductions in plasma sodium and chloride concentrations are common in infectious diseases that primarily affect the large intestine (84). Plasma sodium concentrations of 125 mmol/L are common in calves with clinical coccidiosis, occasionally decrease to 115 mmol/L, and in extreme cases may be 100–105 mmol/L and even below, with similar reductions in plasma chloride concentrations, so that plasma SID remains similar to reference values or is mildly decreased. Another important clinicopathologic difference in bovine coccidiosis to neonatal calf diarrhea is that blood pH and plasma bicarbonate concentrations are usually minimally decreased (83).

There do not appear to be any standardized clinical studies on the response to intravenous fluid administration in calves with coccidiosis. The reported clinicopathological changes in clinical coccidiosis suggest that a NaCl solution would provide the preferred intravenous fluid for calves with plasma sodium concentration < 125 mmol/L; however, the potential for calves with coccidiosis to have severe chronic hyponatremia (i.e., plasma sodium concentrations below 115 mmol/L for at least 24 h) raises concern over the rapid return of plasma sodium concentrations to reference values, which has been associated with pontine demyelinization in other species, and possibly manifest as "nervous coccidiosis" in treated calves. A practical "two buckets" approach to fluid therapy in calves with coccidiosis has therefore been developed. The plasma sodium concentration is measured in the morning and two buckets are placed in the stall for calves with plasma sodium concentration > 125 mmol/L; one that has plain water, and a second bucket that contains 150 g of NaCl per 10 L (sodium concentration, 256 mmol/L). Calves with clinical coccidiosis usually prefer the water bucket containing NaCl and their plasma sodium concentration gradually returns to the reference range. Calves with a plasma sodium concentration < 125 mmol/L are best treated intravenously over the following 24 h with a NaCl solution that has a sodium concentration 10–15 mmol/L higher than the measured plasma concentration. The calf stall should contain only one bucket of water with no added NaCl. This process is repeated each morning until the plasma sodium concentration is > 125 mmol/L, at which time intravenous fluid therapy is discontinued and the "two buckets" approach is implemented. Oral electrolyte solutions formulated for calves with neonatal diarrhea are unsuitable for oral rehydration of calves with clinical coccidiosis as these solutions generally contain insufficient amounts of sodium to correct hyponatremia and furthermore contain considerable amounts of carbohydrates and alkalinizing agents, neither of which are required or indicated in these patients.

INTRAVENOUS FLUID THERAPY IN NEONATAL CALVES WITH SEPSIS

Sepsis and septic shock have been documented to be associated with clinically relevant cardiovascular changes in humans and domestic animals. In children, septic shock is now defined as "*severe infection leading to cardiovascular dysfunction, including hypotension, need for treatment with a vasoactive medication, or impaired perfusion*" (85). This is differentiated clinically from sepsis-associated organ dysfunction that represents "*severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction*" (85). The cardiovascular changes include a relative or absolute decrease in central blood volume, systolic and diastolic alterations of left ventricular and right ventricular function, marked peripheral vasodilation accompanied by systemic hypotension, and increased vascular permeability (86). Studies in neonatal calves with naturally acquired sepsis [(86); **Figure 9**] or experimentally induced endotoxemia [(87–89); **Figure 10**] indicate that impaired cellular metabolism and circulatory dysfunction, not systolic dysfunction, are the primary clinical abnormalities in septic neonatal calves. Impaired cellular metabolism is characterized by sustained hyperlactatemia, azotemia, hypoglycemia and hypothermia and is most likely due to inadequate nutrient delivery at the cellular level (86). Hyperlactatemia is a biomarker of tissue hypoxia and abnormal cellular metabolism, as well as disease severity and mortality in critically ill humans (90) and domestic animals, including calves and adult cattle (49, 91–93). Circulatory dysfunction in septic calves is characterized by decreased preload, manifest as low left ventricular end diastolic volume due to maldistribution of venous blood (relative hypovolemia), and decreased afterload, manifest as low mean arterial blood pressure (86). Current treatment protocols for septic calves are frequently successful, whereas the treatment success of calves in septic shock is markedly lower and best characterized as poor. Early diagnosis of septic shock in calves is likely to have the greatest impact on improving treatment outcomes.

Veterinarians administering intravenous fluids to calves in septic shock need to adjust standard monitoring and treatment protocols because of the presence of systemic hypotension and maldistribution of venous blood. Recent studies in septic human patients have identified concerns with bolus fluid resuscitation in the first hour (20–40 ml/kg) using isotonic polyionic crystalloid solutions (94–96). This fluid administration protocol is associated with increased mortality due to development of cerebral and pulmonary edema (96), most likely due to increased luminal pressures in capillary beds and increased vascular permeability. Traditional high volume isotonic polyionic crystalloid fluid resuscitation of septic neonatal calves should therefore utilize slower rates of

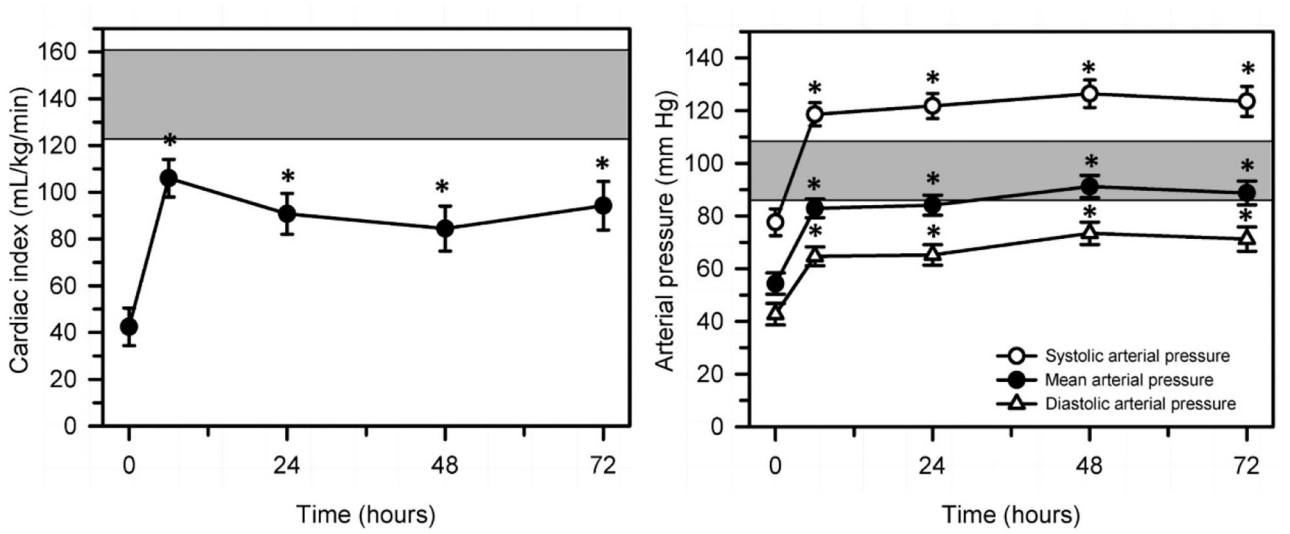

FIGURE 9 | Changes in echocardiographically determined cardiac index (left panel) and systolic, mean, and diastolic arterial pressure (right panel) over 72 h after the start of a standardized treatment protocol in 20 septic calves that included intravenous fluids and vasopressors. Data are presented as least squares mean and SE. The number of calves alive at each measurement time were 20 at 0 and 6 h, 17 at 24 h, 14 at 48 h, and 12 at 72 h. The gray shaded rectangle is the 95% confidence interval for the mean value for 10 healthy calves of similar age and body weight (right panel, mean value for mean arterial pressure). *$P < 0.0125$ compared to time = 0 h value. Reproduced with permission from: Naseri et al. (86).

administration of up to 20 ml/kg BW per hour. Vasopressor therapy (norepinephrine at 10 μg/kg BW/min for 60 min) should be considered in neonatal calves with mean arterial blood pressure < 65 mm Hg after initial fluid therapy (86). More work is needed in this area as the 2020 guidelines for treating hypotensive shock in children in low resource settings recommends administering isotonic crystalloid solutions in the first hour at up to 40 ml/kg, and vasopressor agents (epinephrine or norepinephrine, and possibly vasopressin) for systemic hypotension (85). Fresh whole blood, if available, has theoretical advantages in the initial treatment of septic calves, including improved oxygen delivery (hemoglobin) and buffering (hemoglobin, plasma proteins) as well as increased plasma immunoglobulin concentrations, but contemporary randomized clinical trials using a goal directed resuscitation approach have not been performed in calves.

An alternative strategy would be to administer low volume hypertonic crystalloid fluids for the initial resuscitation of septic calves, particularly those in septic shock. Hypertonic saline solutions (7.2% NaCl, 2,400 mOsm/L, 4 ml/kg BW) have been safely administered to endotoxemic calves, and the rapid intravenous administration of hypertonic saline over 4 min successfully, but transiently, resuscitated calves with experimentally induced endotoxic shock (87, 88). Nevertheless, rapid infusion of large-volume isotonic saline was clinically superior to small-volume hypertonic saline-dextran in calves with experimentally induced acutely endotoxemia (87). A 2014 study in endotoxemic swine evaluated the effect of hypertonic solutions of sodium lactate (11.2%) and sodium bicarbonate (8.4%) at 5 ml/kg per hour administered over 270 min (97). The hypertonic sodium lactate solution increased cardiac output and mean arterial blood pressure while improving oxygenation, relative to hypertonic sodium bicarbonate or isotonic saline (0.9% NaCl). In contrast, a 2016 study in sheep with septic shock, the administration of a hypertonic lactate solution (500 mmol/L) resulted in a shorter survival time than administration of hypertonic saline solution [3.0%; (98)]. The latter finding raises concerns about the use of hypertonic sodium lactate solutions in calves with septic shock. Additional studies appear indicated comparing hypertonic sodium chloride, sodium bicarbonate, and sodium lactate solutions as part of the initial resuscitation of septic calves. Until such studies are completed, isotonic polyionic fluids should be administered intravenously at < 20 mL/kg BW per hour to septic calves, and consideration should be given to administering hypertonic saline (7.2%, 4–5 ml/kg BW over 5 min) intravenously for the initial resuscitation of calves in septic shock.

The supplementation of intravenous fluids with glucose should always be considered in septic calves. Hypoglycemia occurs commonly in septicemic calves with diarrhea due to increased glucose utilization and decreased appetite, and its occurrence is associated with increased mortality (48, 49, 88). The addition of 20 ml of 50% glucose solution to the first liter of the initial intravenous fluid solution (providing 10 g glucose/L of solution and a solution glucose concentration of 56 mmol/L) should be routinely implemented in the initial treatment of septic calves as hypoglycemia is common and associated with mortality in critically ill calves (49). Due to the difficulties in predicting the outcome of intravenous dextrose administration in septic calves, it is advisable to regularly check the blood glucose concentration with a point of care glucometer validated for use in cattle (99). This will permit adjustment of the rate of

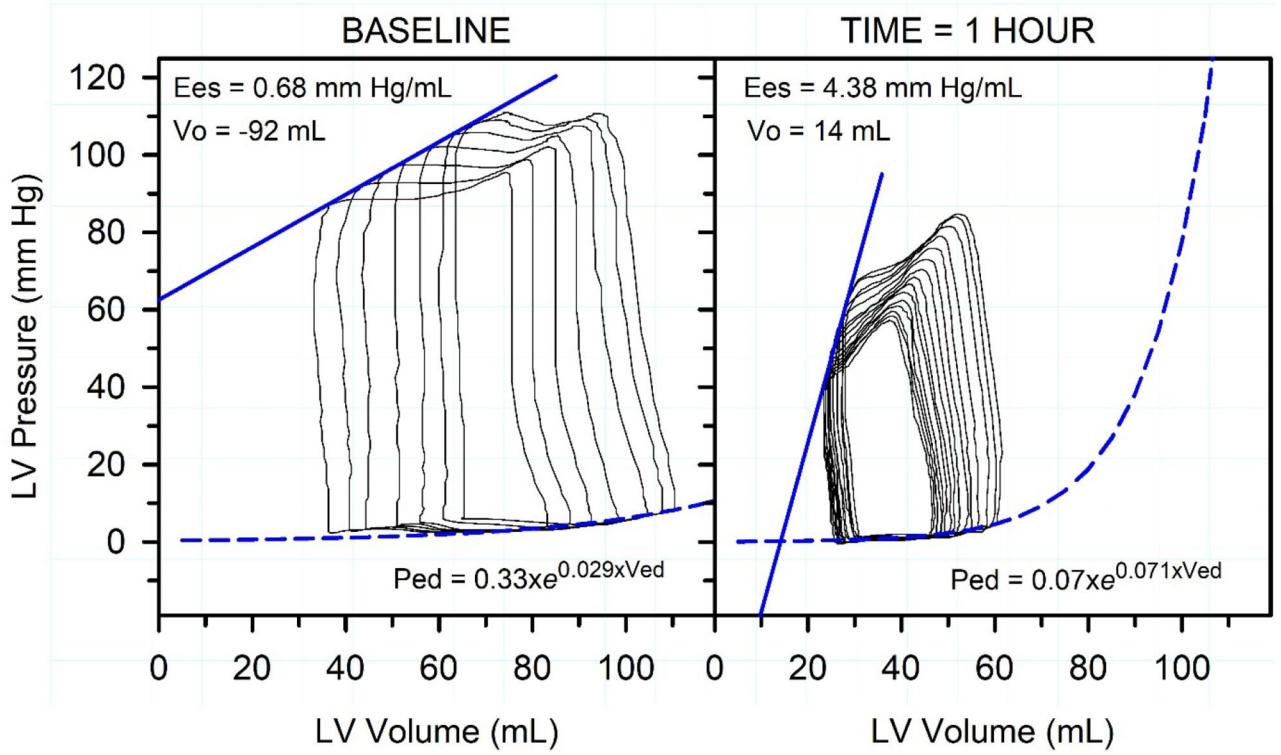

FIGURE 10 | Representative pressure-volume loops, end-systolic pressure-volume relationship (straight blue line), and end-diastolic pressure-volume relationship (dashed exponential blue line) in an endotoxemic calf. Caudal vena-caval occlusion was used to decrease preload while left ventricular (LV) pressure and volume were recorded. The left panel is before endotoxin was administered. The right panel is 1 h after start of endotoxin administration. Note that the administration of endotoxin markedly decreased end-systolic pressure and increased End-systolic elastance (Ees; the gold standard index of cardiac contractility), decreased stroke volume and end-diastolic volume, slightly increased LV diastolic stiffness, and increased heart rate (not shown). The figure indicates that systemic arterial hypotension is the dominant cardiovascular derangement in acute endotoxemia. Reproduced with permission from: Constable (89).

intravenous dextrose infusion with the objective being to restore and maintain euglycemia.

INTRAVENOUS FLUID THERAPY IN ADULT CATTLE

Critically ill adult ruminants differ markedly in their acid-base and electrolyte response to those discussed above in critically ill neonatal calves with diarrhea. Cattle with abdominal diseases that require surgical correction, such as left displaced abomasum, right displaced abomasum, abomasal volvulus, abomasal reflux, small intestinal obstruction, and gastrointestinal hypomotility/atony, are usually dehydrated with the major clinicopathologic changes being a hypochloremic, hypokalemic, metabolic alkalosis due to sequestration of chloride and potassium in the proximal portion of the gastrointestinal tract (38, 100). Moreover, sick lactating dairy cattle, particularly in early lactation, almost always have subclinical hypocalcemia because of the reduction in feed and calcium intake relative to the loss of calcium in milk. As a result of these clinicopathological changes, the preferred intravenous solution in adult cattle should be acidifying and polyionic. An exception to this recommendation is cattle with ruminal acidosis due to excessive consumption of rapidly fermentable starches such as cereal grains that results in metabolic acidosis. Acidemia due to metabolic acidosis can occur in other conditions such as esophageal obstruction (choke), listeriosis with cranial nerve paralysis resulting in excessive loss of saliva by drooling, advanced cases of abomasal volvulus and small intestinal obstructive conditions such as intussception, volvulus or obstruction, and cattle with severe diarrhea or renal failure.

Laboratory evaluation of critically ill cattle is helpful as the magnitude of clinicopathologic abnormalities is difficult to predict based on clinical signs, with the exception being clinical hypocalcemia and clinical hypomagnesemia. However, laboratory evaluation is often unavailable in a timely or low-cost manner, and under these circumstances, the administration of Ringer's solution, 0.9% NaCl or 7.2% NaCl solutions is recommended for correction of the assumed strong ion (metabolic) alkalosis. Subclinical hypocalcemia is rare in sick beef cattle because many examined animals are not lactating, and if they are lactating the milk volume suckled by the beef calf is much lower than the average daily milk production of today's dairy cow.

Ringer's Solution

Ringer's solution should be regarded as the default intravenous fluid for dehydrated adult ruminants, particularly lactating dairy cows, because this intravenous fluid formulation provides the best available solution to treat hypochloremic, hypokalemic, metabolic alkalosis, along with the oral administration of potassium in animals that are inappetent (38, 100). Ringer's solution is an isotonic, balanced, polyionic, acidifying crystalloid solution that contains concentrations of Na (147 mmol/L) K (4 mmol/L), Ca (2 mmol/L), and Cl (155 mmol/L). Ringer's solution is acidifying because its effective SID = 0 mmol/L (**Figure 5**). Intravenous administration of a fluid with a SID of 0 mmol/L will decrease plasma SID (normal SID ≈ 40 mmol/L) and therefore directly decrease plasma pH. At reference values for adult cattle, a 1 mmol/L decrease in SID directly cases a decrease in plasma pH of approximately 0.016 (20, 25).

Intravenous administration of equivolume Ringer's solution and 5% dextrose solutions (16) or equivolume lactated Ringer's solution and 4.4% dextrose solutions (101) have been recommended for rehydrating dehydrated adult cattle. Unfortunately, the former formulation produced a marked hyperglycemia during infusion (plasma glucose concentration peaked at 350 mg/dl) (16) that would be expected to decrease food intake (30) and promote renal diuresis as the plasma glucose concentration exceeds the renal threshold for glucose excretion [(102); **Figure 13**]. Care therefore needs to be taken when adding dextrose to Ringer's solution.

The biggest challenges with administering Ringer's solution to dehydrated adult cattle are the cost and availability of commercial products. Ringer's solution is not available for purchase in North America. In countries where commercial products are available (such as Europe and New Zealand), the price of Ringer's solution per Liter is very high relative to 0.9% NaCl solutions, and the largest volume available is 3 L. Ringer's solution can be formulated at relatively low cost by taking a 5 L bag of 0.9% NaCl and adding the appropriate volumes of commercial products of KCl, $CaCl_2$ dihydrate and sterile water, such that the final solution contains NaCl (8.60 g/L), KCl (0.30 g/L), and $CaCl_2$ dihydrate (0.33 g/L). If large volume administration of Ringer's solution is not practical or economic, a clinically acceptable alternative in adult cattle that can swallow and have some forestomach motility is to administer large intravenous volumes of isotonic saline solution (0.9% NaCl) combined with oral administration of KCl boluses (150 g of KCl) and $CaCl_2$ boluses (50 g of Ca, equivalent to 111 g of $CaCl_2$ or 147 g of $CaCl_2.2H_2O$) (103) or intraruminal administration of similar amounts of KCl and $CaCl_2$ in a suitable volume of water.

Isotonic and Hypertonic Sodium Chloride Solutions

Large volume isotonic saline (0.9% NaCl solution) is clinically inferior to large volume Ringer's solution in treating critically ill adult cattle because 0.9% NaCl solutions have a slightly lower chloride concentration (154 mmol/L) than Ringer's solution (155 mmol/L) and do not include potassium and calcium (9). However, 0.9% NaCl solutions have the advantage of being widely available at low cost in sterile 5 L bags, whereas commercial formulations of Ringer's solution are not available in all countries and must be formulated by the veterinarian.

Following the initial studies of intravenous hypertonic saline in neonatal calves by Constable and colleagues in 1991 (87, 88), the intravenous administration of small volume hypertonic NaCl solutions (7.2%) combined with provision of a large volume OES or water load has been widely adopted for the rapid resuscitation of dehydrated adult cattle (65). The combined treatment protocol provides an inexpensive and practical alternative to the intravenous administration of much large fluid volumes of isotonic saline. Typically, adult cattle are administered 2 or 3 L of hypertonic saline (4–5 ml/kg BW) intravenously over 4–5 min and allowed immediate access to drinking water or an OES (65). The hypertonic saline volume administered to adult cattle is typically 2 or 3 L because most formulations come in 1 L containers; cattle with a body weight range of 400 to 500 kg require 2 L, whereas larger cattle with a body weight range of 600 to 750 kg require 3 L. Intravenous administration of 2 L of hypertonic saline in 5 min can be challenging and requires a 14 g needle and a large pressure head (distance) above the venipuncture site. Intravenous administration of 3 L is very difficult to accomplish within 5 min, and 10–15 min is typically required to administer 3 L in the field without use of an infusion pump. The time taken for administration should be as close to 5 min as possible to obtain the greatest clinical benefit; however, hypertonic saline should not be infused in <5 min because circulatory collapse may occur. The combined treatment of intravenous small volume hypertonic saline and oral large volume water/electrolyte solution rapidly increases plasma volume, increases glomerular filtration rate, and induces a slight metabolic acidosis (65). The volume of hypertonic saline administered should not be increased markedly beyond 4–5 ml/kg BW because infusion of hypertonic saline to euhydrated heifers at 15 ml/kg BW over 15 min resulted in sustained hypernatremia (163 to 170 mmol/L), hyperchloremia (126 to 136 mmol/L) and hyperosmolality (326 to 337 mOsm/kg), without producing any increment in sustained plasma volume expansion (104).

Hypertonic saline is commonly used for the treatment of dairy cattle with endotoxic shock due to coliform mastitis. Small volumes of intravenous hypertonic saline (7.5%, 5 ml/kg BW) increased plasma volume and the cows' voluntary water intake compared to cows treated intravenously with isotonic saline [0.9% NaCl; (105)]. Intravenous hypertonic saline (7.2% NaCl, 2 L over 10 min) has also been administered to cattle with right displaced abomasum, followed by 10 L of 0.9% NaCl IV. The resuscitative effects of this treatment protocol were compared to cattle receiving 26 L of 0.9% NaCl intravenously; the latter volume represented an equivalent sodium load to hypertonic saline treated cows. The initial rate of resuscitation was faster with hypertonic saline compared to conventional large volume fluid administration, based on increases in plasma volume and mean central venous pressure, (106).

Intravenous hypertonic saline (7.5% NaCl, 5 ml/kg over 15 min) was administered to cattle with experimentally induced acute grain overload (ruminal acidosis), and the resuscitative

effects compared to that provided by large volume isotonic saline solution (0.9% NaCl). An equivalent response to both fluids was evident, except that there was a slightly larger decrease in jugular venous blood pH and urine pH in cattle treated with hypertonic saline (107, 108). In addition, hypertonic saline treatment increased glomerular filtration and thereby increased the renal excretion of total lactate by 3.5 times that of isotonic saline treatment, resulting in a lower plasma concentration of total lactate (108). It should be noted on theoretical grounds that intravenous hypertonic saline should be less efficacious in ruminants with acute ruminal acidosis. Rumen osmolality is markedly increased in acute ruminal acidosis, decreasing the osmotic gradient that is generated following rapid IV small volume hypertonic saline administration and therefore the free water volume that is osmotically translocated from the forestomach (7).

Isotonic and Hypertonic Sodium Bicarbonate Solutions

The base excess in cattle with ruminal acidosis that are recumbent or weak and able to stand approximates−20 mmol/L. The estimated bicarbonate deficit in 450 kg body weight cattle exhibiting severe clinicals signs of ruminal acidosis is 3,375 mmol (25 mmol/L × 450 kg BW × 0.3 L/kg BW), assuming an extracellular fluid volume of 30% bodyweight and a base excess in healthy cattle of 5 mmol/L. Intravenous administration of approximately 20 L of isotonic sodium bicarbonate (1.3%, 155 mmol/L) or 3 L of hypertonic sodium bicarbonate (8.4%, 1,000 mmol/L is the preferred initial treatment of ruminal acidosis in severely affected cattle, followed by the administration of oral alkalinizing solutions. Oral rehydration as commonly practiced in dehydrated adult cattle is not suitable for cattle with acute rumen acidosis due to the pre-existing osmotically driven fluid overfill of the rumen that is present in most cases. Specific studies in adult cattle supporting this statement are lacking, but 6% hypertonic sodium bicarbonate solution provided a superior resuscitative response than 7% hypertonic saline in ewes with acute ruminal acidosis (109), particularly related to increased jugular venous blood pH and plasma bicarbonate concentration. Ewes in both groups also underwent rumen lavage and placement of 5 L of water in the rumen (109). A similar response is likely to occur in adult cattle with acute ruminal acidosis.

ORAL FLUID THERAPY IN NEONATAL CALVES WITH DIARRHEA

A large number of oral electrolyte solutions are commercially available to treat neonatal calves with diarrhea and dehydration. Most preparations are in the form of powders that are mixed with fresh cow's milk, milk replacer or water, although liquid preparations are available. Oral electrolyte solution (OES) formulations vary but typically they contain electrolytes (sodium, chloride, potassium), alkalinizing agents (bicarbonate or its precursor such as acetate, citrate, and propionate or formate, a metabolizable strong anion), components that facilitate sodium absorption (glucose, glycine, acetate, propionate), and substrates that provide additional energy (glucose, acetate, propionate, glycine). The inclusion of potassium in OES formulations is supported by studies demonstrating that acidemia and dehydration can result in potassium depletion in skeletal muscle of neonatal calves (59), and that potassium depletion in diarrheic calves is associated with the duration of disease and therefore the duration of feed intake depression (60, 62). Some OES formulations contain components to facilitate normalization of the enteric bacterial population (7), such as lecithin-coated pectin fiber that decreases the proliferation of *Escherichia coli* and Salmonella spp (110). Much progress has been made since the 1970's in identifying important attributes of an OES for diarrheic calves. The critical issues in formulating the ideal OES for neonatal calves are **osmolality**, **sodium concentration**, the **effective SID** that reflects the concentration of alkalinizing agents, and the **energy content**. The last three factors are intimately tied to the osmolality of the OES and **the abomasal emptying rate**, and therefore the rate of sodium delivery to the small intestine and ultimately the rate of resuscitation.

Strong ions, both cations (positively charged) and anions (negatively charged), can be categorized as metabolizable or non-metabolizable in biological solutions at physiologic pH. The difference between the charge assigned to all non-metabolizable strong cations (usually sodium and potassium) and non-metabolizable strong anions (usually chloride) in an OES as fed is called the effective SID (111). The alkalinizing ability of an OES therefore reflects the concentration of strong anions such as acetate, propionate, citrate, that are metabolized to bicarbonate, formate that appears to be metabolized to carbon dioxide, and the concentration of the buffer ion bicarbonate, consequently the alkalinizing ability can be quantified by calculating the effective SID of the fed formulation (46, 111, 112).

It should be noted that the ideal OES formulation for neonatal calves with diarrhea differs markedly from the ideal solution for human infants with diarrhea. The primary difference is that neonatal calves have a much lower ability to sweat in response to a high ambient temperature than human infants. Neonatal diarrhea occurs most commonly in human infants in hot climates, and the additional loss of free water and electrolytes in the infant's sweat means that hypernatremia is a common electrolyte abnormality in human infants with diarrhea, whereas hyponatremia is almost always present in neonatal calves with diarrhea that have not received treatment (25, 49, 57). Consequently, OES formulations for human infants typically have lower sodium concentrations (75 mmol/L) and are hypotonic (245 mOsm/kg).

A general recommendation is to routinely administer an OES to all calves < 21 days of age at the first signs of diarrhea, particularly a more liquid diarrhea; this is because it cannot be accurately predicted how quickly the calf will become dehydrated. For diarrheic calves, the total 24-h fluid requirement for rehydration and subsequent maintenance of euhydration is estimated, with the total fluid requirement typically being 12% of euhydrated body weight or greater per day. Ideally, the 24-h fluid requirement should be given orally in at least 2 feedings; preferably at least three separate feedings (two milk and one OES)

are provided during the first 24 h of treatment and thereafter in calves with watery diarrhea so that the response to treatment can be monitored.

Intravenous fluids should be administered in addition to an OES in calves that are unable to stand or suckle and in calves that an eye recession of 4 mm or into the orbit (**Figure 1**). Calves with an eye recession of <4 mm and that are able to suckle and stand can be adequately treated with oral electrolyte solutions alone [**Figure 6**; (47)], although the rate of resuscitation is slower than that in calves that also received intravenous fluids [**Figure 7**; (66)].

Osmolality of the Oral Electrolyte Solution

The osmolality of the OES, as fed, is primarily determined by the sodium and glucose concentrations, and should range from isotonic (300 mOsm/kg) to hypertonic (700 mOsm/kg) when administered to neonatal calves. This range in osmolality is considered optimal because hypotonic solutions (<300 mOsm/kg) have insufficient sodium content to address the hyponatremia and decreased extracellular fluid volume present in diarrheic calves. Hypertonic solutions are considered physiologic when fed as the presence of a countercurrent exchange mechanism at the tip of the intestinal villus results in an effective osmolality of approximately 600 mOsm/kg in healthy milk-fed calves (7). A markedly hypertonic OES should theoretically not be fed to calves with severe villous damage, such as neonatal diarrhea caused by rotavirus or coronavirus; however, we cannot currently predict with sufficient accuracy etiologic agent of calf diarrhea on the basis of the physical examination and measurement of fecal pH (7).

The initial treatment of a dehydrated calf should use an OES that is not added to milk replacer because administering an OES in water provides superior plasma volume expansion (113). It should be noted that low osmolality fluids (300 mOsm/kg) have inadequate energy content because they have insufficient glucose and consequently a low osmolality OES should not be fed to calves when milk is withheld. For this reason, a hypertonic OES (∼600 mOsm/kg) is preferred whenever milk is withheld (102, 114). Nevertheless, caution should be applied when administering high osmolality solutions (> 600 mOsm/L) as they decrease abomasal emptying rate (103, 114, 115). This can lead to abomasal bloat and potentially predispose to *Clostridium perfringens* abomasitis. An isotonic OES (∼300 mOsm/kg) should be administered whenever milk is concurrently fed because energy dense milk with an osmolality of ∼300 mOsm/kg is being provided (110, 115). The OES powder should be added to the milk to provide a solution osmolality of ∼600 mOsm/kg, rather than feeding an equivolume mixture of milk and OES, as the latter mixed solution interferes with clot formation in the abomasum and slows the rate of abomasal emptying (116). Ideally, fresh milk should be fed no later than 24 h after the start of treatment to diarrheic calves; fresh cow's milk is preferred to pasteurized waste milk or milk replacer. This is because the energy content of milk is required to maintain body weight, and fresh milk contains trophic factors that facilitate repair of damaged intestinal epithelium (7). In general, milk should not be withheld from diarrheic calves (117), and fresh water must always be provided (118).

Sodium Concentration of the Oral Electrolyte Solution

The OES should contain a sodium concentration of 90 to 130 mmol/L (117). An important reason to administer an OES is to expand the extracellular volume, and this requires adequate sodium intake. It should be noted that the sodium concentration of cow's milk is relatively low with a mean value of 28 mmol/L in healthy quarters (119, 120), and milk cannot provide the sodium intake required in dehydrated calves with diarrhea. Oral electrolyte solutions with sodium concentrations < 90 mmol/L also provide an inadequate sodium load; conversely, sodium concentrations > 130 mmol/L can result in hypernatremia and additional free water loss (7), particularly if mixed into milk replacer solutions that often have a higher sodium concentration than whole milk (121, 122).

Glucose, acetate, propionate, glycine, and citrate facilitates the absorption of sodium from the gastrointestinal tract lumen and at least one of these substances should be included in the OES. Cotransport mechanisms for sodium with glucose, volatile fatty acids, citrate, and amino acids (such as glycine) in the luminal membrane of villus epithelial cells are unimpaired in calves with enterotoxigenic *E. coli* diarrhea and are thought to be partially functional in malabsorptive/maldigestive diarrheas (7). Glycine was a constituent of the first commercially available OES for calves based primarily on its low cost, wide availability, the likelihood of amino acid coupled sodium transport in the calf's small intestine, and because glycine was included in the first oral rehydration solutions for human infants. The clinical importance of glucose-coupled and glycine-coupled sodium absorption in an OES for diarrheic calves remains uncertain.

The results of a study in euhydrated calves suggested that the importance of glucose-coupled sodium transport in rehydrating calves with diarrhea should be re-evaluated as the ratio of glucose to sodium may not be an important component of treatment efficacy in neonatal calves (123, 124). Additional studies are needed to determine the optimal glucose-to-sodium ratio of an OES for calves; currently the recommended range between 1.0 and 3.0 with an optimum ratio of 1.4 is derived from studies in human infants. It is likely that calves with mild diarrhea and dehydration could be successfully treated with a low sodium hypotonic OES as the total body sodium deficit and anticipated fecal sodium loss are likely to be low (125). In contrast, it is likely the calves with moderate diarrhea and dehydration would benefit from being administered an isotonic OES with a higher sodium concentration, as the total body sodium deficit and anticipated fecal sodium loss are likely to higher (125).

Effective SID of the Oral Electrolyte Solution

The effective SID of an OES is thought to approximate 40–80 mmol/L because calves with a watery or chronic diarrhea typically have a strong ion (metabolic) acidosis due to the presence of hyponatremia, normochloremia, and varying degrees

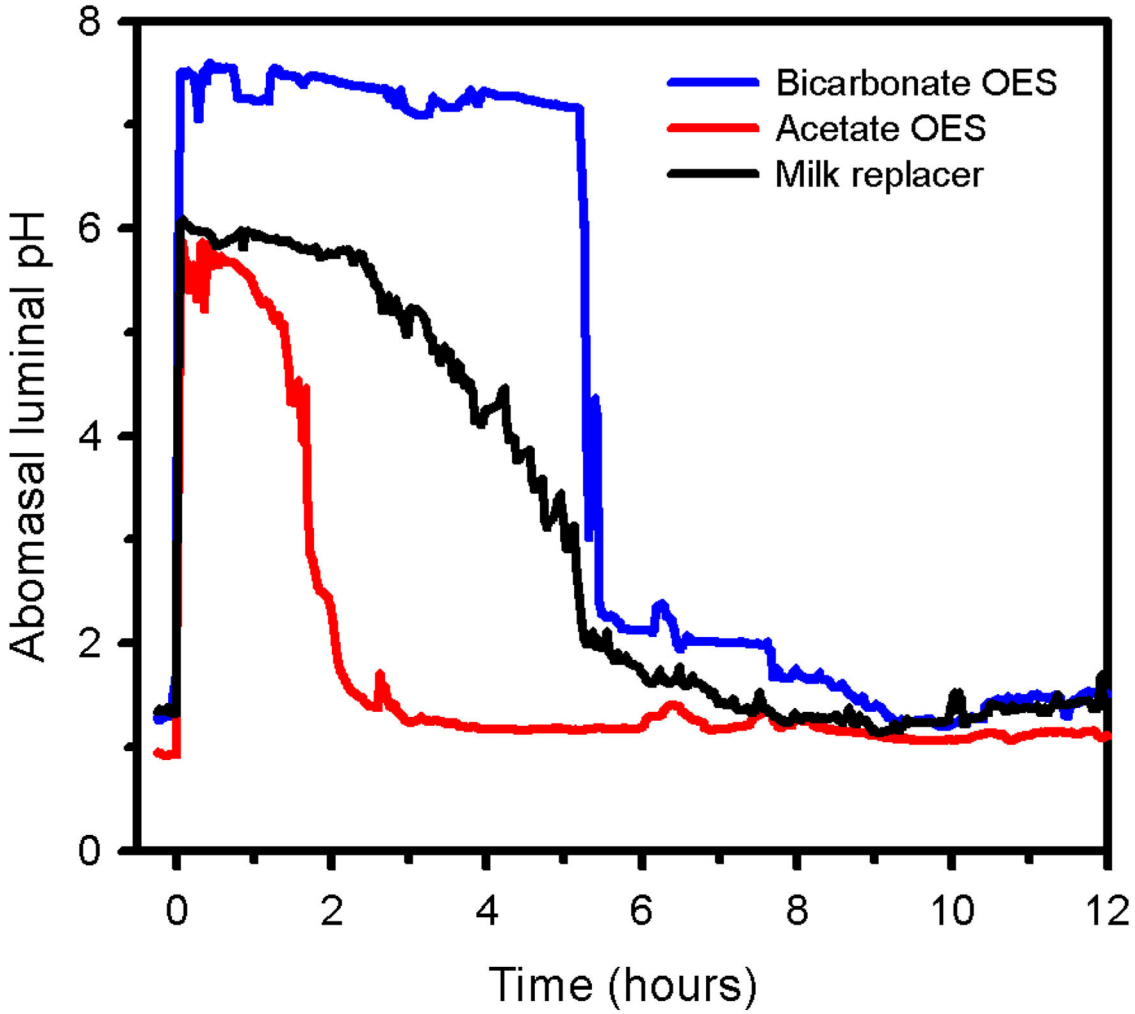

FIGURE 11 | Abomasal luminal pH in a healthy dairy calf suckling an all-milk protein milk replacer (solid black line), a hypertonic high-bicarbonate oral electrolyte solution (OES, blue line), or an isotonic acetate- and propionate-containing OES (red line) in random order at 0 h. Note that the isotonic acetate- and propionate-containing OES is emptied much faster than milk replacer and a hypertonic high-bicarbonate OES. Also note that the hypertonic high-bicarbonate OES causes a marked and sustained increase in abomasal luminal pH. Figure from Peter Constable, unpublished.

of hyper D-lactatemia (25, 126, 127). Oral electrolyte solutions with an effective SID = 0 mmol/L create a systemic strong-ion acidosis after being absorbed, and consequently these solutions are not recommended for treating dehydrated calves with diarrhea because they do not contain an alkalinizing agent. Solutions with an effective SID = 0 mmol/L provide an inferior resuscitative response in calves with watery diarrhea to solutions that contain an alkalinizing agent and have an effective SID of at least 40 mmol/L (126). Typical electrolyte and acid-base changes in calves with mild to moderate diarrhea where the fecal characteristics are characterized as soupy have not been well defined, particularly for the first few days of diarrhea in calves with normal appetites for milk.

The OES for calves with watery diarrhea should contain one or more alkalinizing agents, such as bicarbonate, acetate, propionate, formate, or citrate, at a total concentration range of 40 to 80 mmol/L that reflects an effective SID of 40 to 80 mmol/L (114, 128–131). An effective SID of 60 mmol/L may be optimal (129) and has been adopted by the European Union (130). Bicarbonate-containing solutions are the most effective at rapidly correcting severe acidemia in neonatal calves with diarrhea; however, a theoretical disadvantage of a bicarbonate-containing OES is that they increase abomasal pH and therefore have the potential to decrease the ability to form a milk clot in the abomasum as clotting requires a low abomasal pH [(112); **Figure 11**]. This theoretical disadvantage does not appear to be true, at least when an OES with bicarbonate concentrations of 25 mmol/L (117), 49 mmol/L (132) or 62 mmol/L (133) are fed in conjunction with cow's milk. A second disadvantage of a bicarbonate containing OES, when fed without milk, is excessive alkalinization of the abomasum (**Figure 11**), thereby decreasing the effectiveness of low abomasal pH in killing

ingested enteric pathogens (9). Of potential clinical significance is that acetate and propionate inhibit growth of Salmonella spp, whereas bicarbonate does not inhibit growth of Salmonella in the intestinal lumen (7).

Acetate, propionate, and citrate must be metabolized from the strong metabolizable anion to bicarbonate to exert an alkalinizing action (117). Acetate and propionate metabolism could be impaired in severely acidemic or dehydrated calves, although this has not been proven. Acetate or propionate can be administered with milk as they do not raise abomasal pH or inhibit the clotting of milk. Citrate complexes Ca^{2+} and consequently inhibit clotting as calcium is needed for milk clotting.

Rate of Abomasal Emptying

The rate of rehydration in dehydrated calves depends upon the rate that an OES is delivered to the small intestine where fluid is absorbed, and the latter is dependent on the rate of abomasal emptying (7). Interestingly, the abomasal emptying rate is decreased in diarrheic calves when milk or an OES is suckled (133–135). The two most important determinants of emptying rate are the volume and caloric content of an ingested meal (114). The type of protein or fat, osmolality, and duodenal pH also influence abomasal emptying rate, with the rate being decreased when a high OES osmolality is fed or luminal pH is <2.0 or >10.0 (102, 114).

Suckling or esophageal intubation of a high-glucose OES provides a slightly slower rate of abomasal emptying and plasma volume expansion than suckling a low glucose OES (102). Oral electrolyte solutions that provide >2.4 g of glucose/kg BW per day slow the rate of plasma volume expansion and are therefore not recommended for rehydration (102).

Energy Content of the Oral Electrolyte Solution

It is now widely accepted that milk should continue to be fed to diarrheic calves while they are receiving an OES, provided that water is readily available to treated calves (118). Historically, milk was withheld from diarrheic calves for 1–2 days and then gradually reintroduced over the next few days. The rationale for milk withholding was the loss of lactase in epithelial cells damaged by common enteropathogens such as rotavirus, coronavirus, and *Cryptosporidium parvum* (7), impairing the calf's ability to digest milk. Feeding an OES alone, even those containing high glucose concentrations, does not provide sufficient energy to the calf and hypoglycemia develops within 8–16 h of feeding the OES and withholding milk [(136), **Figure 12**]. Feeding milk in addition to an OES shortens the number of days with diarrhea while increasing weight gain and fat stores, and a faster rate of repair of damaged intestinal mucosa than in calves deprived of milk (110).

Moderate to high glucose containing OES should not be administered to diarrheic calves that are also consuming fresh milk or milk replacer as the calves already have adequate energy intake, particularly if the main alkalinizing agent in the OES is propionate. The additional glucose load in these calves may lead to intestinal fermentation if unabsorbed, or glycosuria if hyperglycemia exceeds the renal threshold [140–160 mg/dl] for glucose in neonatal calves [**Figure 13**, (102)]. This would be accompanied by the additional loss of free water in the feces or urine (121, 122). Whether an OES should contain agents such as glutamine or butyrate that have the potential to assist in repairing damaged intestinal epithelium is being actively researched.

ORAL FLUID THERAPY IN ADULT CATTLE

Orally administered sodium is exceptionally well-absorbed in adult cattle (typically oral bioavailability estimates are 90%), and sodium absorption is accompanied by the passive movement of water from the forestomach into the extracellular space (7). Both sodium and water must be absorbed to increase the extracellular fluid volume, with active sodium transport mechanisms in the forestomach accounting for approximately half of the sodium absorbed each day in healthy cattle (9). Maintenance fluid requirements should be administered orally only to adult cattle with normal gastrointestinal motility as oral administration of large fluid quantities to cattle with rumen atony results in ruminal sequestration of fluid and a slower rate of absorption. Although dehydrated cattle with forestomach hypomotility or atony appear to clinically benefit from ororuminal administration of large OES volumes, intravenous fluid administration (including hypertonic saline treatment) is preferred in the initial resuscitation of sick dehydrated cattle with forestomach atony.

The optimal OES formulation for dehydrated cattle is unknown. It is currently believed that an effective OES should contain sodium, potassium, and chloride at a minimum, as dehydrated cattle with decreased feed intake frequently have a hypochloremic, hypokalemic metabolic alkalosis (38). Propionate could be added to the OES as a source of glucose once absorbed and to promote sodium absorption; however, sodium propionate is not as soluble in water as other sodium salts and its inclusion will require a larger administration volume. Calcium, magnesium, and phosphate are often added to the OES in cattle suspected to have mild hypocalcemia, hypomagnesemia, or hypophosphatemia, respectively (9). A variety of oral formulations are commercially available that are dissolved in water and administered via an orogastric tube to adult cattle. These products aim to correct or prevent common electrolyte imbalances of adult cattle but in general are based on empirical evidence while disregarding important aspects of oral rehydration therapy in cattle. Combining salts may provide a convenient supplementation method, but dissolved salts can react with each other, potentially resulting in poorly soluble compounds and a decrease in their oral bioavailability. Such reactions occur when calcium- or magnesium salts are combined with phosphate salts (137–139). Supplemented minerals can furthermore alter the absorption efficiency of other minerals from the digestive tract as they interfere with their transport mechanisms. Such interactions have been described for potassium impairing the transruminal transport mechanisms of magnesium, or sodium reducing the absorption efficiency of potassium from the rumen.

The osmolality of orally administered fluids should be hypotonic if rehydration is an important clinical goal; however,

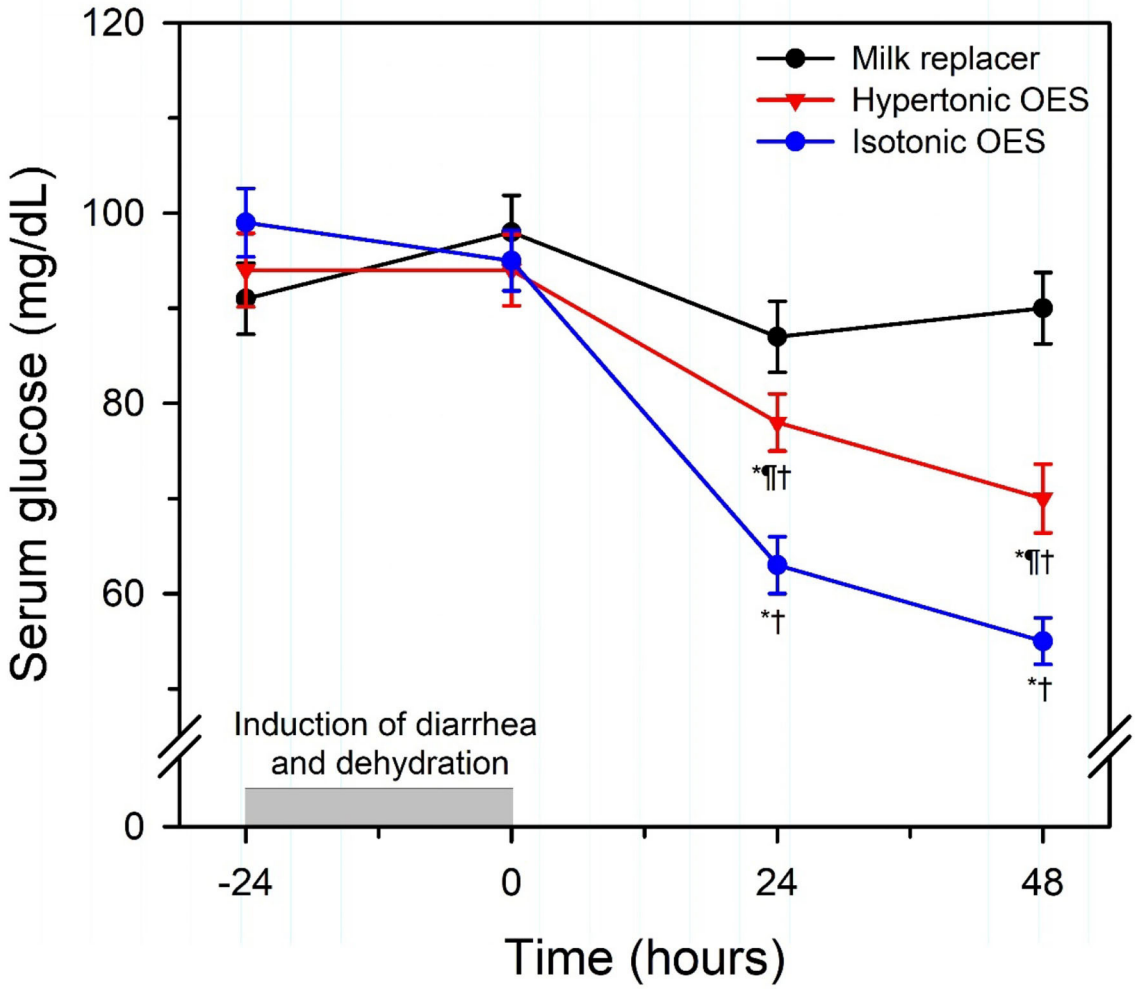

FIGURE 12 | Serum glucose concentrations in neonatal calves with experimentally induced diarrhea and dehydration, and response to oral administration (2 L of solution at 12 h intervals) of milk replacer ($n = 6$), a hypertonic oral electrolyte solution (OES; osmolarity = 606 mOsm/L; glucose = 330 mmol/L; $n = 6$), or an isotonic OES (osmolarity = 307 mOsm/L; glucose = 85 mmol/L; $n = 6$). Note that continued feeding of milk replacer maintained serum glucose concentrations, whereas serum glucose concentration was decreased in calves fed a high glucose or low glucose OES. Values expressed as mean ± SD. *$P < 0.05$, compared to time = 0 value; †$P < 0.05$, compared to Group M value at the same time interval; ¶$P < 0.05$, compared to Group I value at the same time interval. Reproduced with permission from: Constable et al. (136).

the upper range of tonicity that is safe to administer has not been determined. Estimating the effect an oral drench solution will have on the rumen fluid osmolality requires not only taking into consideration the amount of a salt administered but also the solubility of the salts administered. The solubility of salts in formulations developed for oral administration to adult cattle vary and this is rarely taken into consideration. A net flow of water from rumen to plasma occurs whenever rumen osmolality in adult cattle is > 20 mOsm/kg lower than plasma osmolality, and the rate of water movement from rumen to plasma increases as rumen osmolality decreases (140). Oral electrolyte administration should therefore not produce hyperosmotic rumen fluid, as this will cause free water to move from the extracellular space into the rumen, thereby increasing rumen volume, decreasing the extracellular fluid volume, and increasing the severity of clinical dehydration. Hyperosmotic rumen fluid is the main reason for dehydration in ruminants with ruminal acidosis (grain overload). However, a hypertonic OES requires a lower fluid volume to administer and the added osmolar load should result in additional voluntary water intake by the animal.

One recommended OES formulation for adult cattle, particularly cattle with hypochloremic, hypokalemic, metabolic alkalosis, contains 7 g of NaCl, 1.25 g of KCl, and 0.5 g of $CaCl_2$ per L of water, equivalent to 140 g NaCl, 25 g KCl, and 10 g $CaCl_2$ in 20 L of water (11). This provides an OES containing 120 mmol/L of NaCl, 16.8 mmol/L of KCl, and 4.5 mmol/L of $CaCl_2$, with a calculated osmolarity of 287 mOsm/L. An

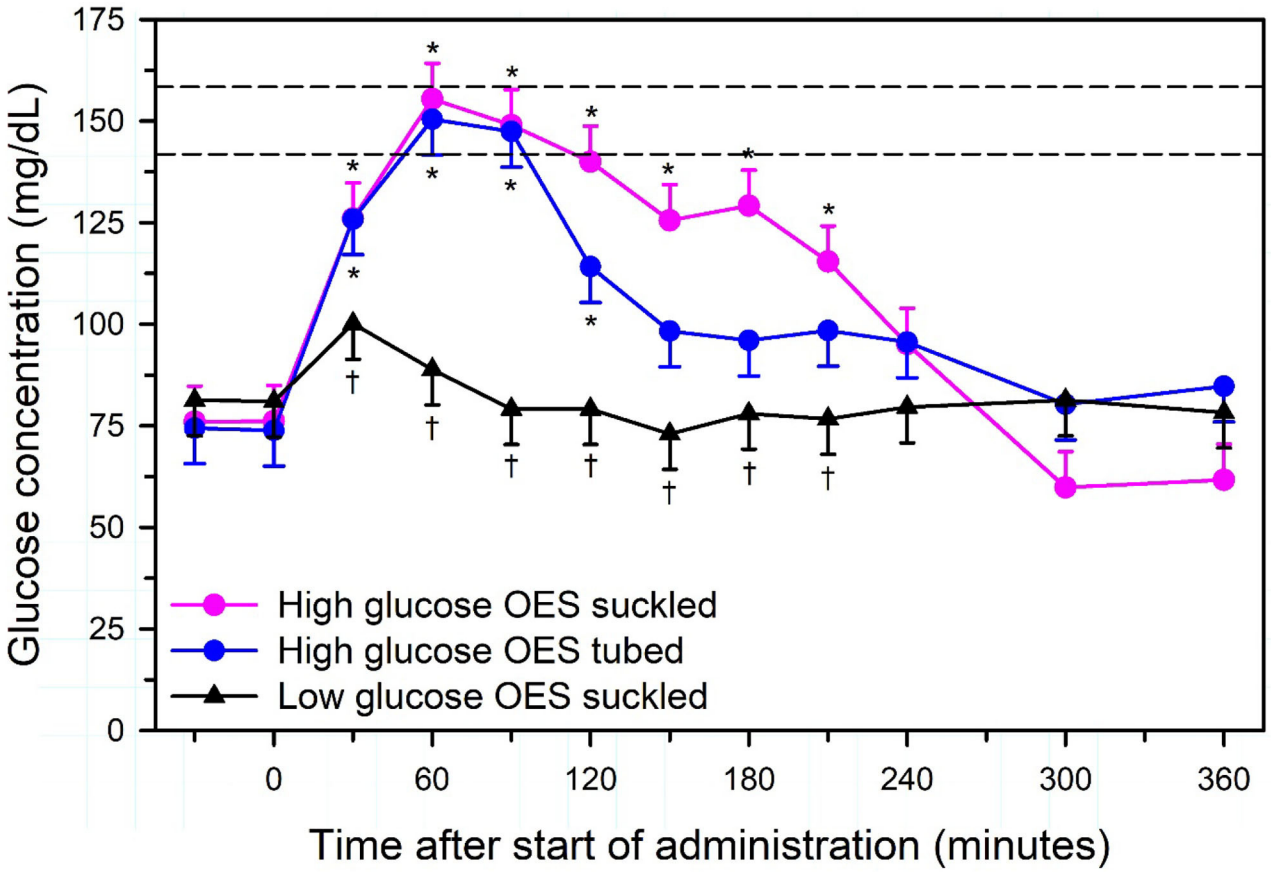

FIGURE 13 | Change in plasma glucose concentration (least squares mean ± standard error) in seven calves that were administered 2 L of a high-glucose oral electrolyte solution (OES; glucose = 405 mmol/L) by suckling or esophageal intubation, or 2 L of a low-glucose OES (glucose = 56 mmol/L) by suckling. The horizontal dashed lines indicate the range of values (140–160 mg/dl) for the renal threshold for glucose in neonatal calves. An asterisk (*) indicates significantly different from the time = 0 min value. A dagger (†) indicates significantly different from the value for the high-glucose OES suckled group at the same time. Reproduced with permission from: Nouri and Constable (102).

alternative formulation contains 4 g of NaCl, 1 g of KCl, 2 g of $CaCl_2$, and 0.5 g of $MgCl_2$ per L of water (141), providing an OES containing 120 mmol/L of Na, 13.4 mmol/L of K, 36 mmol/L of Ca, 11 mmol/L of Mg, and 128 mmol/L of Cl, with a calculated osmolarity of 257 mOsm/L. It should be noted that both formulations contain much less KCl than that recommended (up to 0.4 g of KCl/kg BW for the first 24 h) for treating hypokalemia in adult cattle (142, 143).

Although a minimum volume of 20 L is recommended when administering oral fluids to adult cattle, larger fluid volumes (40 or 60 L) can be safely administered to large adult cattle or cattle with marked dehydration. Rumen volumes in adult cattle typically comprise 13 to 17% of bodyweight (144), equivalent to 104 to 136 L in large cattle (800 kg body weight). In one study, adult beef cattle (420 kg body weight) had water withheld for 3 days while being housed in hot dry conditions; these cattle voluntarily drank 63 L of water in 20 min without any overt clinical signs (145). Ororuminal administration of large volumes of water runs the risk of acute hyponatremia and hypoosmolality due to an osmotically driven translocation of water from the forestomach into the extracellular space. It is therefore preferable to administer hypotonic solutions instead of pure water, and intraruminal administration of 60 L of water containing 250 g of sodium chloride provides a half-isotonic solution with a calculated osmolarity of 142 mOsm/L. It should be noted, however, that ruminants are physiologically adapted to rapidly drink very large water volumes. This is because large water volumes are effectively retained in the rumen due to the increased secretion of hypotonic saliva (145), decreasing the risk of acute hyponatremia. Nevertheless, caution should be exercised when administering large volumes of hypotonic solutions or water to adult cattle, as ororuminal administration of cold solutions could result in cold shock to ruminal microorganisms and hypothermia, and hypoventilation or regurgitation of liquid contents and aspiration pneumonia could occur in cattle with pre-existing ruminal distention.

Oral administration of a sufficient quantity of sodium salts with a high effective SID cause a metabolic alkalosis (strong-ion alkalosis) in adult ruminants, similar to neonatal ruminants. Oral sodium bicarbonate administration provides a useful adjunct

treatment in adult ruminants with ruminal acidosis and D-lactate acidosis due to grain overload, as the oral administration of sodium bicarbonate (2.5 g/kg BW) is alkalinizing in adult cattle (146, 147). An important need in fluid and electrolyte therapy for adult ruminants is formulation of a practical, effective, and inexpensive OES.

AUTHOR'S NOTE

The authors have completed a large number of research studies related to intravenous and oral fluid therapy in neonatal calves and adult cattle.

AUTHOR CONTRIBUTIONS

All authors listed have been actively engaged in fluid therapy in neonatal calves and adult cattle for at least 10 years and made substantial intellectual contributions to the work. All authors have approved the manuscript for publication.

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REVIEW
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Fluid Therapy in Dogs and Cats With Sepsis

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Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis may occur secondary to infection anywhere in the body, and its pathogenesis is complex and not yet fully understood. Variations in the host immune response result in diverse clinical manifestations, which complicates clinical recognition and fluid therapy both in humans and veterinary species. Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Although septic shock is a form of distributive shock, septic patients frequently present with hypovolemic and cardiogenic shock as well, further complicating fluid therapy decisions. The goals of this review are to discuss the clinical recognition of sepsis in dogs and cats, the basic mechanisms of its pathogenesis as it affects hemodynamic function, and considerations for fluid therapy. Important pathophysiologic changes, such as cellular interaction, microvascular alterations, damage to the endothelial glycocalyx, hypoalbuminemia, and immune paralysis will be also reviewed. The advantages and disadvantages of treatment with crystalloids, natural and synthetic colloids, and blood products will be discussed. Current recommendations for evaluating fluid responsiveness and the timing of vasopressor therapy will also be considered. Where available, the veterinary literature will be used to guide recommendations.

Keywords: sepsis, septic shock (MeSH), fluid therapy, critical care—small animal, immunopathogenesis

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INTRODUCTION

Sepsis is one of the most important causes of morbidity and mortality in human medicine and is associated with high mortality rates in dogs and cats. Globally, more than 30 million human patients are diagnosed with sepsis each year; 5 million of them die, with a high economic burden and long-term morbidity affecting the survivors (1, 2). The prevalence and incidence of sepsis in veterinary medicine are not well-documented. Available data show that in dogs, mortality rates associated with septic peritonitis range from 21 to 68% (3–5). Other reports indicate mortality rates of 70% for dogs that experience organ failure (6). In cats with sepsis, mortality rates of 40% have been documented (7). Based on these results and others, it appears likely that sepsis is a major cause of mortality in hospitalized dogs and cats.

Vascular alterations, damage to the endothelial glycocalyx, hypoalbuminemia, and myocardial dysfunction are important pathophysiologic consequences of sepsis and complicate decision-making in regards to fluid therapy. Patients may present with varying degrees of illness severity, and may or may not manifest all of these pathophysiologic consequences of sepsis. Ultimately,

fluid therapy in these patients must tailored to each individual, taking into account their relative intravascular volume, interstitial hydration, fluid responsiveness, and cardiac function.

DEFINITION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). It may occur with infection anywhere in the body, and may be secondary to bacterial, fungal, or viral agents. Septic shock is further defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone (1). These definitions represent our most current understanding of sepsis and accompany a change in the clinical recognition of sepsis in human medicine. Prior to 2016, sepsis was clinically recognized by the presence or suspicion of infection together with at least 2 out of 4 systemic inflammatory response syndrome (SIRS) criteria (**Table 1**). The SIRS criteria may be fulfilled secondary to a multitude of causes, with infection being only one of them. In human patients with sepsis, the SIRS criteria have been found to lack both sensitivity and specificity for organ dysfunction, and a cutoff value of 2 does not necessarily represent an increased risk of mortality (8). Concerns over the failure of the SIRS criteria to adequately identify patients with infections that have increased risk of mortality, as well as the focus of these criteria on inflammation as opposed to a dysregulated host response, have prompted new clinical criteria for sepsis. Sepsis is now recognized as the presence or suspicion of infection in conjunction with evidence of organ dysfunction per the sequential organ failure assessment (SOFA) score (**Table 2**), and the "quick" SOFA (qSOFA) score (**Table 3**) has been proposed as a screening tool for sepsis in patients housed outside of the ICU (1). Septic shock is clinically recognized by the need for vasopressors to maintain normotension or by a serum lactate >2 mmol/L in patients without hypovolemia (1). Significant controversy regarding these changes exists in human medicine, particularly surrounding the use of qSOFA, and whether or not updated definitions are needed in veterinary medicine is an open question. As of this time, the SIRS criteria are still used to diagnose sepsis in dogs and cats, as no consensus regarding a change in the clinical recognition of sepsis has been reached in veterinary medicine. The SIRS criteria in dogs and cats were respectively derived from a cohort of surgical patients and a small necropsy study, and may not be representative of all small animal patients with sepsis (9, 10). That said, the presence of SIRS in dogs and cats should raise the practitioner's index of suspicion that sepsis may be present; however, if a patient is clinically

TABLE 1 | The systemic inflammatory response syndrome (SIRS) criteria in dogs, cats, and humans.

	Dogs (2/4 required)	Cats (3/4 required)	Humans (2/4 required)
Temperature (°F)	<100.6 or >102.6	<100.0 or >104.0	<96.8 or >100.4
Heart rate (beats/min)	>120	<140 or >225	>90
Respiratory rate (breaths/min)	>20	>40	>20
White blood cell ($\times 10^3/\mu l$); % bands	<6 or >16; >3%	<5 or >19	<4 or >12; 10%

TABLE 3 | The "quick" SOFA (qSOFA) score in humans.

Criteria	Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

If the cutoff for each parameters is met, the patient is assigned 1 point, so that the total score can range from 0-3 points. A score of ≥2 indicates organ dysfunction.

TABLE 2 | The sequential organ failure assessment (SOFA) score in humans.

	0	1	2	3	4
PaO_2/FiO_2 ratio	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets ($\times 10^3/\mu l$)	≥150	<150	<100	<50	<20
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Creatinine (mg/dl) Urine output (ml/day)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5.0 <200

Each parameters is given a score of 0–4, so that the total score can range from 0 to 24.

deteriorating yet does not meet the requisite number of SIRS criteria, sepsis should still be considered as a differential.

PATHOPHYSIOLOGY OF SEPSIS

The following sections on pathophysiology will briefly focus on the most important abnormalities leading to organ failure and fluid leakage during sepsis and septic shock, including the receptors involved in the activation of the inflammatory response and the complement cascade, neutrophil and platelet dysfunction, and immunosuppression. The microcirculatory and hemodynamic abnormalities involving endothelial cells will be addressed in detail elsewhere (Chapter 4).

Initiation of the Inflammatory Response

Fundamentally, the host immune response is designed to localize, confine, and destroy pathogens while repair mechanisms are activated. Sepsis is a dysregulated form of this response, and alterations can manifest as endothelial cell damage, coagulopathies, microcirculatory and hemodynamic alterations, metabolic and neuroendocrine immune network abnormalities, endoplasmic reticulum stress, autophagy, and many other pathophysiological processes leading to vascular leakage and organ failure. Early in the inflammatory response, the innate immune system is activated upon the recognition of pathogen and host cell molecules by a subset of germline-encoded pattern recognition receptors (PRRs) (11, 12). These receptors can be found in the extracellular and subcellular compartments, such as the cellular and endosomal membranes and the cytosol; in secreted forms present in the bloodstream and interstitial fluids; and in intracellular vesicles, such endosomes and lysosomes (13, 14). The sensing of microorganisms by PRRs, regardless of their location, relies on recognizing molecules frequently found in pathogens or host cell products. The PRR superfamily has four major sub-families: the toll-like receptors (TLRs); NOD-like receptors; the retinoic acid-inducible gene 1 (RIG-1)–like receptors; and the C-type lectin receptors (15). Pattern recognition receptors engage pathogen-associated molecular patterns (PAMPs), which are conserved structures in invading organisms that serve to identify these organisms as foreign, or damage-associated molecular patterns (DAMPs), which are endogenous molecules, such as mitochondria that are released or modified by sterile insults, such as trauma (14, 16–18). Circulating nucleic acids, either DNA or RNA derived from pathogens or host cells, are also strong activators of PRRs (19). Intracellular PRRs are activated by signaling cascades originated by extracellular PRRs (20). During a response, nucleic acids are an important target for innate immune recognition, as all microbial pathogens depend on their DNA and/or RNA for replication. Cells and other sensor systems of the innate immune system expressing PRRs include neutrophils (21), macrophages (22), dendritic cells (23), platelets (24), complement system (25), natural killer cells (26), fibroblasts (27), and some epithelial cells, such as those of the intestinal tract (28). In a host, cells of the immune system expressing PRRs, as well as those of sensor systems, such as the complement system, can initiate both proinflammatory and anti-inflammatory responses. The intracellular signaling process is complex, with numerous signaling pathways, ultimately leading to multi-gene expression, which is involved in adaptive immunity and inflammation. Recent data on gene activation during sepsis show that in human septic patients, a total of 910 unique genes are differentially expressed (29). This study also revealed that 43 functional cellular pathways that were closely associated with inflammation and response to infection were activated during sepsis. The inflammatory response is an essential step in activating the immune system to the presence of infection so that cells from the innate response can rapidly locate and mount an effective defense against pathogens (30). This defense is typically well-organized, with the inflammation under control after the infection is resolved. After this, the immune system can prime itself for an effective immune response to future infection (31). If the response becomes dysregulated, both the hyperinflammatory and the hypoinflammatory responses can lead to many of the sequela that are observed in sepsis and septic shock. Among these are disseminated intravascular coagulation (DIC), multi-organ dysfunction, and peripheral vasodilation leading to hypotension and subsequent organ hypoperfusion (32, 33).

Local and Systemic Inflammatory Response

The host–pathogen interactions at the site of injury or infection, neutrophils, resident macrophages, and dendritic cells coordinate the initial inflammatory response through PAMP–PRR and DAMP–PRR signaling. Downstream, this pathway activates the inflammasome response, a multiprotein intracellular complex that includes enzymes, such as caspase-1 (34). The inflammasome pathway in neutrophils and macrophages triggers the production and secretion of the highly proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 (35). During activation, neutrophils become autophagic, and other cell-death mechanisms are also activated and integrated into the host's defense against bacteria (36). These mechanisms regulate the generation of the proinflammatory immune response (37). Pathogen- and damage-associated molecular patterns may also directly activate receptors on neutrophils, which induce migration and recruitment into infection sites (38). Neutrophils—key cells in sepsis—display a wide range of effector mechanisms to counteract pathogens, which include phagocytosis, the production of reactive oxygen species, and killing of ingested pathogens by proteases (39). Activated neutrophils release neutrophil extracellular traps (NETs), which are webs of DNA and antimicrobial proteins designed to kill pathogens and aid in pathogen clearance (40). Excessive NET formation promotes inflammation and tissue damage during sepsis. Exosomes also play an important role in amplifying the inflammatory response. Exosomes are extracellular vesicles released by cells, such as neutrophils, macrophages, and platelets, and participate in local and systemic intercellular communication (41). The proinflammatory effects of exosomes are mediated by cytokines (e.g., IL-1α, IL-1β, IL-6, IL-18, TNF-α), miRNA, DAMPs, and NETs contained within the vesicles. The vesicles activate neutrophils, macrophages,

and endothelial cells. Macrophages interact with bacterial products, as previously described for neutrophils, and release proinflammatory cytokines (e.g., TNF-α and IL-6), which contribute to vascular endothelial dysfunction, increased vessel diameter, and leakiness, the latter leading to fluid and immune cell infiltration of the surrounding tissues (42). The excessive amounts of proinflammatory cytokines produced by these cells lead to a hyperinflammatory state called the cytokine storm (43). This process is part of the dysregulation of the immune system during sepsis and is characterized by high levels of circulating IL-6 and IL-10 and the decreased ability of monocytes, macrophages, and dendritic cells to produce hyperinflammatory cytokines, such as TNF-α and interferon gamma (IFN-γ) in response to PAMPs and DAMPs. Current evidence suggests that in dogs with sepsis, there is a dysregulated proinflammatory cytokine production. In one study, numerous cytokine levels were measured in dogs with sepsis and compared to healthy dogs and those with non-infectious systemic inflammation (44). The results showed that the levels of the pro-inflammatory cytokines IL-6 and IL-8 and several chemokines (CXCL-8, keratinocyte-derived chemokine, and CCL2), and high-mobility group box-1 (HMGB-1) were higher in dogs with sepsis than in the healthy controls. An interesting finding in the study was that CCL2 was found to be predictive of poor survival. It should be pointed out that HMGB-1 is a DAMP that activates the innate responses of TLR2 and TLR4 (45). In humans with sepsis, the presence of HMGB-1 has been associated with poor outcomes (46). Another study compared levels of proinflammatory cytokines in dogs with naturally-occurring *Babesia rossi* infection to healthy controls and found that dogs with babesiosis experienced a similar proinflammatory cytokine storm, which correlated with the disease severity (47).

Sepsis and Septic Shock

There are two basic components in sepsis, which combine to form a continuum of events between hyper-inflammation and hypo-inflammation. The role of neutrophils and platelets during the development of sepsis and septic shock as well as the most important mechanisms leading to immunosuppression will be addressed. Sepsis develops when the immune response to an infection becomes generalized and involves normal tissues remote from the site of an injury or infection. It is characterized by a systemic dysregulated host response to infection in which there are simultaneous hyperinflammatory and hypo-inflammatory states driven by the dysfunction of both the innate and adaptive immunity. An early hyperinflammatory phase in which the cytokine storm progresses is accompanied by the compensatory anti-inflammatory response syndrome to limit the tissue damage (48). How the early and acute hyperinflammatory phase transitions to the chronic or late hypo-inflammatory phase as sepsis progresses to septic shock is not fully understood. What is known is that some of the most important determinants of immunoparalysis are macrophage deactivation, negative regulatory mediators, such as programmed cell death-1 (PD-1), increased apoptosis (with a decrease in T cell counts), increased suppression of immune cells, increased production of anti-inflammatory cytokines, and alterations in energy production leading to cell anergy (49). During the late phase of sepsis and in septic shock, there are numerous hemodynamic, microcirculatory, cellular, and metabolic abnormalities that cause increased mortality and morbidity in affected patients (50). In general terms, the most important circulatory damage leading to multi-organ dysfunction is induced in part by the activation of the complement cascade and impairment in both platelets and neutrophils, including the excessive production of NETs (51). Dysregulated activation of the complement cascade, which is a tightly regulated multiprotein complex and a major component of the innate immune response, is designed to detect, destroy, and clear invading pathogens as well as amplifying the inflammatory response (52). Pathogen destruction is mediated by the lytic complement component—the membrane attack complex (MAC), which also causes injury to endothelial cells (53). Under normal conditions, bystander cells have a protective mechanism against the MAC: CD59 (54). With downregulation of CD59 and dysfunctional regulators, there is excessive activation of the MAC, causing bystander endothelial cells in the microcirculatory space to be damaged and inducing multi-organ dysfunction (55–57).

During septic shock, neutrophils play a pivotal role. They experience highly dysregulated functions, including the recruitment of immature cells, impaired migration, inefficient pathogen recognition (leading to impaired bacterial control), tissue damage, and cell margination (58). These alterations trigger an endothelial cell dysfunction that leads to increased permeability and fluid leakage from the intravascular space to the interstitium (59). Neutrophils lose elasticity and become more rigid, resulting in the altering of their migration through endothelial tight junctions (60). This excess rigidity in the cells is responsible for capillary occlusion, which itself is involved in multiple organ failure (59). Organ damage is enhanced as the lifespan of neutrophils is increased compared to those of neutrophils associated with non-septic inflammation, and these mature neutrophils are less likely to return to the bone marrow, promoting the margination of dysfunctional cells in the capillary networks (61). Neutrophils produce excessive NETs, which, in turn, activate the coagulation cascade, leading to immunothrombosis (62).

Immunothrombosis is the interaction between coagulation and innate immunity that triggers a generalized disseminated intravascular coagulation (DIC). It is important to note that there are other factors involved in coagulation in sepsis, such as monocytes and macrophages activated by invading microorganisms and their components (63). Coagulation activation also becomes dysfunctional (64). Additionally, during septic shock, inflammation stimulates capillary sequestration *of neutrophils* by activating circulating forms of these cells, which cells are responsible for further occlusion of the small vessels as well as the migration of vital organs and the release of cytotoxic substances (proinflammatory cytokines, proteolytic enzymes) that are involved in tissue damage and multiple organ failure, as shown in a study conducted by Mantovani et al. (65).

Platelets also are important contributors to organ failure during septic shock, as they actively participate in microvascular and mitochondrial dysfunction, DIC, acute kidney injury, and

cardiac dysfunction (66). Recently published data show that activated platelets have a dual role in the immune response. First, they can engage the innate mechanisms of defense by directly killing pathogens as well as facilitating pathogen clearance by activating macrophages and neutrophils. Second, they promote NETs with the formation of platelet aggregates and disseminate microthrombi, which can be a risk factor for mortality (67). As a consequence, platelets promote endothelial damage, thrombosis, and organ failure. There are several mechanisms by which platelets can induce microvascular dysfunction during septic shock. In addition, they possess procoagulant properties that result in widespread microvascular coagulation and sepsis-induced disseminated intravascular coagulation. The nature of the thrombo-inflammatory response lies in the intense cross talk that takes place between platelets, neutrophils, and NETs and that results in widespread intravascular coagulation, microvascular occlusion, and ischemic and cytotoxic organ damage (68).

A state of induced immunosuppression normally predominates over the proinflammatory response, often starting during the early onset of septic shock (69). There are several mechanisms involved in the induction of the immunosuppression. These include a dysregulated compensatory anti-inflammatory response (70), increased apoptosis of T and B cells (lymphocyte exhaustion) (71), immune paralysis (increased tolerance to endotoxins) (72), and dysregulated expansion of T-regulatory cells. *Immune paralysis* refers to a state consisting of the reduced ability to trigger an immune response to a pathogen. Macrophages have decreased expression of antigen-presenting capabilities, with a reduction of important monokines that are required for an immune response (72). Another late feature of septic shock is the reprogramming of macrophages to an anti-inflammatory M2 phenotype, all of which is an attempt to decrease inflammation but which results in defective pathogen destruction caused by phagocytic cells (73). During septic shock, lymphocyte exhaustion occurs as the effector function of T and B cells is impaired. There is sustained and increased expression of inhibitory immune checkpoint molecules on exhausted T-cell surfaces and an increased expression of the PD-1 receptor and ligand (PD-L1) (63). Recent studies have demonstrated that peripheral blood polymorphonuclear neutrophils (PMNs) from septic patients express high levels of PD-L1 (74). These cells exhibit a decline in their capacity to phagocytize bacteria; therefore, sepsis drives altered PMN function. A consequence, the syndrome contributes to the increased risk of secondary and opportunistic infections and late death associated with sepsis and septic shock (70).

IMPLICATIONS FOR FLUID THERAPY

Generation of Cardiovascular Alterations

Cardiovascular dysfunction in septic shock involves both peripheral vascular dysfunction and myocardial alterations. There are several mechanisms involved, from dilation of the veins and arteries to the dysregulated innate immune response affecting the endothelium and microcirculation. One mechanism in particular is the increased permeability of the intravascular space to the interstitium leading to tissue fluid loss and relative hypovolemia, which reduces ventricular diastolic function (75). It has been documented in humans that sepsis-induced myocardial dysfunction occurs in about 25–50% of patients with septic shock (76). The activation of the Toll-like receptors by PAMPs/DAMPs triggers the inflammatory cascade, as described in the preceding sections (77, 78). Once the inflammasome has been activated, the production of inflammatory cytokines is triggered. The release of chemotactic cytokines and intercellular adhesion molecules, such as ICAM-1 attracts neutrophils and macrophages from the microvessels to the myocardium, where they adhere (79, 80). Cell activation and the inflammatory response impact the coordination of the depolarization of the cardiomyocytes and subsequent calcium release, leading to decreased cardiomyocyte contractility. Complement activation also plays a key role in septic cardiomyopathy. Complement fragment 5a (C5a) is a potent anaphylatoxin (81). The presence of dysregulated amounts of C5a activates receptors C5aR1 and C5aR2 (present in cardiac myocytes), resulting in defective action potentials. In addition, alterations are induced by C5a, such as changes in the intracellular calcium homeostasis and electrophysiological functions that, when induced, result in defective action potentials in cardiomyocytes and the activation of neutrophils leading to dysregulated NET production (82). It should be pointed out that the NETs are composed of histones, which also cause defective action potentials, and the buildup of reactive oxygen species. The activated complement cascade will generate a membrane complex attack, which causes pore formation in cells, both in pathogens as well as in hosts cells, such as endothelial cells. This action will trigger endothelial dysfunction, including the production of microthrombi and DIC (57).

Vascular Alterations

Sepsis results in a loss of vasomotor tone in the resistance vessels, resulting hypotension despite normal or increased cardiac output. This sepsis-induced vasoplegia affects both the arterial and venous circulation. Arterial vasodilation results in a relative hypovolemia and subsequent hypotension, reducing oxygen delivery to tissues. Venodilation occurs in the splanchnic and cutaneous vascular beds, resulting in an increase in unstressed volume and consequent decreased venous return and cardiac output (83). In addition, endothelial damage and microvascular thrombosis results in a reduced functional capillary density and abnormal microcirculatory flow (57). The ultimate goal of fluid therapy in patients with poor perfusion is to increase tissue oxygen delivery; however, these vascular alterations result in a maldistribution of blood flow. Although fluid resuscitation may increase the stressed volume in these patients and result in improvement in macrocirculatory parameters (e.g., blood pressure), microcirculatory alterations may persist and the goal of increasing oxygen delivery may remain unfulfilled.

Endothelial Glycocalyx

The endothelial glycocalyx is a gel-like substance comprised of proteoglycans, glycoproteins, and glycosaminoglycans that lines the endothelium and regulates vascular permeability. The endothelial glycocalyx also plays a role in vascular relaxation by transmitting shear stress to endothelial cells which then

produce nitric oxide, thus contributing to vasodilation (84). See Chapter 4 for further discussion of the functions of the endothelial glycocalyx.

In patients with sepsis, the endothelial glycocalyx is thought to be degraded, and this degradation has been associated with increases in TNF-α, IL-1β, IL-6, and IL-10 (84). Thinning of the endothelial glycocalyx results in alterations in vascular permeability, resulting in intravascular fluid loss and tissue edema. Additionally, fluid therapy may further damage the endothelial glycocalyx and hypervolemia has been associated with degradation in experimental models (84). However, a human study of patients with sepsis found that total crystalloid volume infused was not associated with shedding of an endothelial glycocalyx component (syndecan-1), suggesting that fluid volume does not contribute to endothelial glycocalyx damage in sepsis (85).

Albumin is not contained within the endothelial glycocalyx as it is repelled by the negatively-charged glycosaminoglycans, but does accumulate on the luminal surface (86). When the endothelial glycocalyx is damaged, this layer of albumin is reduced as well, further contributing to a decrease in capillary oncotic pressure. Evidence suggests that administration of albumin-containing fluids (e.g., serum albumin solutions or fresh frozen plasma) may be protective to the endothelial glycocalyx as albumin carries erythrocyte-derived sphingosine-1-phosphate to the endothelium, where it suppressed matrix metalloproteinase activity (84).

Hypoalbuminemia

Hypoalbuminemia occurs in sepsis for a plethora of reasons, including downregulated hepatic production, gastrointestinal and/or renal losses, decreased protein intake, and leak through a damaged endothelial barrier. Our improved understanding of microvascular function and the revised Starling's forces (see Chapter 2) have led to the appreciation that there is no resorption of fluid at the venule end of the capillary, the so-called "no absorption rule." Thus, the old paradigm of administering colloids (natural or synthetic) to hypoalbuminemic patients to reduce edema and "pull" fluid into the vasculature no longer holds true. Although the administration of colloid solutions may not redistribute fluid into the intravascular space, hypoalbuminemia decreases the capillary oncotic pressure and may also contribute to endothelial glycocalyx damage, both of which may worsen interstitial edema.

Myocardial Dysfunction

Sepsis-induced myocardial dysfunction has been well-documented in humans, and is characterized by decreased systolic function (87). Typically when there is decreased contractility, there is diastolic compensation, and the left ventricular end diastolic volume is increased, which helps to preserve stroke volume and therefore cardiac output. However, in many human patients with sepsis, there is decreased diastolic compliance as well (87). It is unclear why some patients with sepsis develop diastolic dysfunction, but it is associated with increased morbidity (87). Patients that have myocardial dysfunction may be less responsive to fluid therapy, and patients with decreased contractility may require administration of positive inotropes to increase cardiac output. These patients may also be less tolerant of intravenous fluids and prone to congestive heart failure, requiring more caution with fluid therapy.

CURRENT RECOMMENDATIONS

Fluid Resuscitation

Patients with sepsis frequently present with hypotension, which may be secondary to relative hypovolemia from vasodilation, absolute hypovolemia from gastrointestinal or renal losses, or myocardial dysfunction. Fluid therapy is considered a cornerstone of sepsis treatment, in addition to antimicrobials, source control, and frequently, vasopressors. The complexity of the disease process combined with variation in illness severity and presentation have made the formulation of guidelines that apply to all patients difficult, and clinically it is often challenging to determine how much fluid should administered.

One of the most well-known trials that addressed resuscitation in human patients with sepsis is the Early Goal Directed Therapy (EGDT) trial by Rivers et al. (88). This single-center study randomized 263 patients with sepsis or septic shock to receive either EGDT or standard care for the first 6 h of hospitalization (87). Patients in both groups received a combination of IV fluids and vasopressors to achieve a mean arterial pressure (MAP) of 65 mmHg or greater, a central venous pressure (CVP) of 8–12 mmHg, and a urine output (UOP) of 0.5 ml/kg/h or greater (87). Patients in the EGDT group also had resuscitation endpoints of a central venous oxygen saturation ($ScvO_2$) $\geq$70% and a hematocrit $\geq$30%, and a dobutamine infusion was used to increase cardiac output if CVP, MAP, and hematocrit were optimized by $ScvO_2$ remained lower than 70% (87). Patients in the EGDT group received more IV fluids, blood transfusions, and dobutamine, and had a significantly lower mortality rate compared to the standard care group (30.5 vs. 46.5%, $p = 0.009$) (87). These findings led to widespread adoption of protocolized EGDT, and in 2004 EGDT was added to the Surviving Sepsis Campaign (SSC) guidelines (89). However, since the publication of this study, three larger multicenter trials comparing a protocolized EGDT to standard care have been performed: ProCESS, ARISE, and ProMISE (90–92). These trials failed to show a mortality benefit of EGDT over standard care; however, in each of these trials illness severity was lower and patients were enrolled later in hospitalization compared to the Rivers trial, which may in part explain why the protocolized care was less effective. In veterinary medicine, a resuscitation protocol using blood pressure, $ScvO_2$, CVP, lactate, base deficit, and hematocrit was evaluated in 30 dogs with sepsis or septic shock secondary to pyometra (93). $ScvO_2$ and base deficit were the best predictors of non-survival, but this protocol has not been compared to other resuscitation strategies to determine if there is a mortality benefit of using such a protocol (93).

The current SSC guidelines recommend administration of 30 ml/kg of crystalloid within the first hour of resuscitation of sepsis-induced hypoperfusion, as evidenced by organ dysfunction, hypotension, or increased lactate (94, 95). This volume of fluid has a low quality of evidence to support it, and was adopted

primarily because it is considered usual practice in the early stages of resuscitation (93). Indeed, these recommendations have been met with some controversy (96). It is difficult to recommend this as a standard in veterinary medicine, given the lack of evidence for this volume of fluid in humans as well as species-specific differences in blood volume and fluid tolerance. Given the heterogeneity of clinical presentations and varying degrees of concurrent hypovolemia in cats and dogs, an individualized, patient-based approach would appear reasonable. In patients with evidence of hypoperfusion and without concurrent cardiac disease, a strategy of incremental isotonic crystalloid fluid boluses (10–15 ml/kg) can be used, with reassessment of the patient's status to determine if they are fluid responsive. Dynamic measures of fluid responsiveness, such as the passive leg raise (PLR) have proven to be better predictors of fluid responsiveness than static parameters, such as CVP and $ScvO_2$; however, PLR has not been adopted in veterinary medicine due to the anatomic differences between humans and dogs and cats (97). Other dynamic variables used to identify fluid responsiveness, such as pulse pressure variation and systolic pressure variation are useful in patients undergoing mechanical ventilation with a set tidal volume, but have little use in the majority of veterinary patients. For further discussion of monitoring for fluid responsiveness, see Chapter 19.

If the patient is not responsive to IV fluids and remains hypotensive, administration of a vasoactive medication is indicated. Norepinephrine (0.1–1 mcg/kg/min) is the vasopressor of choice in the treatment of septic shock, and early use in resuscitation has been associated with improved hemodynamics (83, 89, 98). Although definitions of early administration vary, recent evidence in humans with septic shock suggests that administration of norepinephrine within the first few hours of septic shock confers a mortality benefit (99). Norepinephrine acts on both α- and β-adrenergic receptors, although its actions on α-adrenergic receptors predominate, causing primarily vasoconstriction. This not only increases arterial vascular tone, but causes venoconstriction as well, resulting in a decrease in unstressed volume and an increase in venous return and cardiac output (99). Evidence suggests that norepinephrine may also improve microvascular flow in septic shock (100). If decreased systolic function secondary to myocardial depression is present, dobutamine (5–15 mcg/kg/min) can also be considered as a positive inotrope.

Maintenance

Following resuscitation, many patients with sepsis require ongoing intravenous fluid therapy due to both decreased intake as well as ongoing losses, particularly if the gastrointestinal tract is the source of sepsis. The goal of ongoing fluid therapy is to maintain euhydration, which may be difficult. This is in part due to altered vascular permeability and hypoalbuminemia, both of which contribute to increased leak of fluid from the intravascular to the interstitial space. Additionally, critically ill patients frequently experience increased ADH secretion, resulting in fluid retention (101). In human patients with sepsis, net positive fluid balance is common and each 1L of cumulative fluids at 72 h of hospitalization has been associated with an increased odds of mortality (102). Individual patient fluid needs should be assessed frequently (every 4–6 h), using physical examination and body weight. Clinical signs of fluid overload include increasing body weight, serous nasal discharge, increased respiratory rate and effort, peripheral edema, body cavity effusions, chemosis, and jugular venous distention. If point-of-care ultrasound is available, serial monitoring for the presence of effusions, B-lines indicating alveolar-interstitial syndrome, and left atrial enlargement can be extremely useful in identifying fluid overload prior to the onset of clinical signs. For further discussion of fluid overload, see Chapter 20.

Although enteral water is never appropriate for treatment of hypoperfusion, it may be used to provide maintenance water to patients that no longer require resuscitation. If the patient is willing to drink, water can be provided by mouth. In patients that are unwilling or unable to drink and are unable to tolerate IV fluids, a nasogastric tube can be placed to administer water. Any water that is provided via the enteral route should be measured and recorded, so that it can be factored into a comprehensive fluid plan.

Fluid Types

Crystalloids

Crystalloid solutions are the mainstay of fluid therapy in patients with sepsis, and balanced solutions are preferred over unbalanced solutions. One of the first large trials comparing balanced crystalloids (lactated Ringer's solution [LRS] and Plasmalyte A) to 0.9% sodium chloride in 15,802 critically ill humans was the SMART trial (103). A secondary analysis of 1,641 patients with sepsis in this trial found that patients in the balanced crystalloid group had lower mortality (26.3 vs. 31.2%, adjusted odds ratio 0.74; 95% confidence interval [CI], 0.59–0.93; $p = 0.01$), a greater number of vasopressor-free days (20 ± 12 vs. 19 ± 13; aOR, 1.25; 95% CI: 1.02–1.54), and a lower incidence of adverse renal events within 30 days (35.4 vs. 40.1%; aOR, 0.78; 95% CI: 0.63–0.97) (104). Although this effect is seen in patients without sepsis, it appears to be greater in patients with sepsis (102). Administration of high chloride fluids, such as 0.9% sodium chloride is thought to induce renal vasoconstriction and subsequent acute kidney injury (105). High chloride fluids have also been shown in experimental sepsis models to increase TNF, IL-10, and IL-6 concentrations and to impair microcirculatory function compared to balanced crystalloids (106, 107). The underlying pathogenesis of these differences is an ongoing area of investigation.

Synthetic Colloids

The use of synthetic colloids, such as hydroxyethyl starch (HES) is controversial, and has generally fallen out of favor in patients with sepsis. The VISEP trial evaluated 537 human patients with sepsis and found that there was a higher rate of acute kidney injury and need for renal replacement therapy in patients treated with 10% HES (200/0.5) compared to LRS (108). Conversely, the CRYSTMAS trial compared 6% HES (130/0.4) to 0.9% sodium chloride in 196 human patients with sepsis and found no difference in renal values or mortality between the groups; however, this study was small and may have been underpowered to detect a difference (109). The 6S trial compared 6% HES

(130/0.42) to Ringer's acetate in 798 patients with sepsis and found increased 90 day mortality as well as increased need for renal replacement therapy in the HES group (110). A Cochrane review of HES compared to other fluid therapies concluded that there is an increased risk of acute kidney injury and need for renal replacement therapy in all patients treated with sepsis, and an increased risk of renal injury based on RIFLE (Risk, Injury, Failure, Loss of renal function, End-stage kidney disease) criteria in septic vs. non-septic patients (111). It is difficult to know if this information can be extrapolated to veterinary patients, as there are species-specific differences in HES metabolism. In addition, dogs and cats with sepsis are typically hospitalized for shorter durations compared to human patients, and receive far less total colloid. Several retrospective studies have evaluated HES use in dogs with conflicting results, although none have specifically evaluated a population of dogs with sepsis (112–114). Two retrospective studies in non-azotemic cats failed to show an association between HES administration and acute kidney injury or mortality (115, 116). In one of these studies, cats with sepsis were specifically evaluated and there was no HES-associated acute kidney injury noted; only 14 cats were in this group and the authors cautioned against making recommendations until a larger group of septic cats could be evaluated (115). Given that there is no clear survival advantage for synthetic colloids in patients with sepsis and there is potential risk of renal injury, use of these fluids in this patient population is not recommended. For further discussion of the controversies surrounding synthetic colloids, see Chapter 7.

Albumin

Hypoalbuminemia is common in patients with sepsis, and has been associated with poor prognosis in both humans and dogs (3, 117, 118). Despite this, it is unclear whether this is a marker of disease severity or a contributor to morbidity and mortality. It is also unclear whether or not albumin transfusion results in improved outcomes, although evidence suggests that it may improve mortality in patients with septic shock. Several human studies have evaluated the effect of albumin transfusion in critically ill patients. The SAFE study was a multicenter, randomized, double blind trial comparing 4% human serum albumin (HSA) to 0.9% sodium chloride over 28 days in 6,997 human ICU patients (119). Overall, there was no difference in mortality, organ failure, or length of stay between the groups (116). However, in the subset of patients with sepsis, there was a trend toward decreased mortality in patients that received albumin compared to 0.9% sodium chloride (30.7 vs. 35.5%, RR 0.87, 95% CI: 0.74–1.02, $p = 0.09$) (116). As a result of this finding, the ALBIOS trial was conducted. This trial was a multicenter, randomized, open label comparison of 20% albumin and crystalloid compared to crystalloid alone in 1,818 adults with sepsis or septic shock (120). Patients that received albumin had a higher mean arterial pressure, a shorter time on vasopressors, and lower net fluid balance. Overall there was no difference in mortality or organ failure between the groups, but a *post-hoc* analysis of the 1,121 patients with septic shock did find lower mortality in the albumin group (RR 0.87, 95% CI: 0.77–0.99, $p = 0.03$), indicating that there may be a benefit to albumin transfusion in this patient population (117).

Evidence supporting albumin transfusion in veterinary medicine is less robust. A retrospective comparison of 25% HSA transfusion to no albumin in 39 dogs with septic peritonitis found that survivors had increasing albumin levels during hospitalization, but albumin transfusion itself was not associated with survival (116). A prospective, randomized trial of 5% canine albumin compared to clinician-directed therapy in 14 dogs with septic peritonitis found that albumin levels remained increased 24 h after transfusion in the albumin group, but the study was not powered to evaluate mortality as an outcome (121). Given the evidence available in humans, it is reasonable to administer albumin to patients in septic shock if crystalloids alone are insufficient for maintaining intravascular volume. Due to the potential for acute and delayed transfusion reactions when administering xenotransfusions, administration of canine albumin is preferable to HSA in dogs. As no species-specific albumin product exists for cats and there is no evidence supporting or opposing albumin transfusion in this species, no recommendations can be given.

Blood Products

In the Rivers trial, patients were transfused with packed red blood cells (pRBCs) to maintain a minimum hematocrit of 30% (87). Due to the adoption of EGDT as standard of care, this transfusion threshold became widespread. In 2014, the TRISS trial was published, which compared a conservative transfusion threshold (hemoglobin <7 g/dl) to a more liberal threshold (hemoglobin <9 g/dl) in patients with septic shock (122). This multicenter trial found that patients in the conservative group received a median of 1 unit of pRBCs compared to 4 units in the liberal group, and that there was no difference in mortality or ischemic events in either group (3). This suggests that a lower transfusion threshold is reasonable in patients with septic shock.

Fresh frozen plasma (FFP) is not indicated in patients with sepsis unless a concurrent coagulopathy with evidence of bleeding is present. Interestingly, FFP transfusion has been found to decrease both TNF-α and sydencan-1 levels in critically ill human patients, 45% of which had sepsis (123). This suggests that FFP may decrease both inflammation and endothelial glycocalyx degradation. Although FFP may potentially have a role in disease states with altered endothelial glycocalyx integrity, the clinical implications of this are unknown, and further research is warranted.

CONCLUSION

Sepsis is a complex syndrome that may result in vascular alterations, hypoalbuminemia, and myocardial dysfunction, complicating fluid therapy decisions. Fluid therapy plans should be individualized to each patient based on their clinical condition, taking into consideration whether or not there is evidence of hypoperfusion, vasoplegia, hypoalbuminemia, or cardiac dysfunction present. Balanced crystalloid solutions

are the mainstay of fluid therapy, although care must be taken to limit edema formation. In patients that are not fluid responsive, norepinephrine should be considered early. Synthetic colloids are not recommended due to the risk of renal injury. If profound hypoalbuminemia and hypotension are present, albumin transfusion can be considered.

AUTHOR CONTRIBUTIONS

FM contributed the pathophysiology section. BL contributed the definitions, implications for fluid therapy, and recommendations sections. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Volume Resuscitation in the Acutely Hemorrhaging Patient: Historic Use to Current Applications

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Acute hemorrhage in small animals results from traumatic and non-traumatic causes. This review seeks to describe current understanding of the resuscitation of the acutely hemorrhaging small animal (dog and cat) veterinary patient through evaluation of pre-clinical canine models of hemorrhage and resuscitation, clinical research in dogs and cats, and selected extrapolation from human medicine. The physiologic dose and response to whole blood loss in the canine patient is repeatable both in anesthetized and awake animals and is primarily characterized clinically by increased heart rate, decreased systolic blood pressure, and increased shock index and biochemically by increased lactate and lower base excess. Previously, initial resuscitation in these patients included immediate volume support with crystalloid and/or colloid, regardless of total volume, with a target to replace lost vascular volume and bring blood pressure back to normal. Newer research now supports prioritizing hemorrhage control in conjunction with judicious crystalloid administration followed by early consideration for administration of platelets, plasma and red blood during the resuscitation phase. This approach minimizes blood loss, ameliorates coagulopathy, restores oxygen delivery and correct changes in the glycocalyx. There are many hurdles in the application of this approach in clinical veterinary medicine including the speed with which the bleeding source is controlled and the rapid availability of blood component therapy. Recommendations regarding the clinical approach to volume resuscitation in the acutely hemorrhaging veterinary patient are made based on the canine pre-clinical, veterinary clinical and human literature reviewed.

Keywords: hemorrhage, resuscitation, trauma, coagulopathy, shock

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INTRODUCTION: HISTORIC APPROACH TO HEMORRHAGING PATIENT

Acute hemorrhage in small animals results from traumatic and non-traumatic causes. While there are differences in overall patient management depending on the cause of the acute blood loss, systemic effects associated with volume of blood loss are repeatable. Co-morbidities associated with acute loss of intravascular volume and oxygen carry capacity are related to the proportion of blood volume lost and compensatory reserve of the individual patient (1, 2). While the physiologic response is predictable, resuscitation of the acutely hemorrhaging patient has dramatically shifted over the years, typically as a result of war-time medical efforts.

In human medicine, acute hemorrhage and its sequelae are the leading cause of preventable death in military and civilian settings (3). Over the last century, the approach to fluid resuscitation of the bleeding patient has gone through many iterations, frequently fueled by battlefield lessons, including whole blood transfusion (WWI), component therapy (WWII), synthetic and natural colloid fluids (Korean War), large volume crystalloid (Vietnam), back to whole blood (Iraq/Afghanistan conflicts) and coagulation testing guided component therapy (4, 5).

This review seeks to describe current understanding of the resuscitation of the acutely hemorrhaging small animal veterinary patient through evaluation of pre-clinical canine models of hemorrhage and resuscitation, clinical research in dogs and cats, and selected extrapolation from human medicine. It is recognized that mechanism-based reasoning for interventions in veterinary medicine predominate clinical decision making in the absence of large randomized clinical trials and systematic reviews of the clinical literature (6). Additionally, similar to austere environment challenges in human medicine, timing and availability of volume resuscitation resources in the acutely hemorrhaging small animal veterinary patient can vary significantly. Efforts to address these challenges and proposed solutions are addressed.

DEFINITION OF PROBLEM AND CAUSES

For the purposes of this review article, patients experiencing acute blood loss are divided into 5 categories based on the cause of bleeding and the patient's hemostatic status upon arrival to a veterinary care facility (**Table 1**).

Traumatic Injury Causing Blood Loss, Non-coagulopathic

These are patients that have sustained injury from an external force (blunt and/or penetrating) leading to blood loss that can vary from minor to catastrophic. Source of blood loss can occur externally (e.g., lacerations, bite wounds), intracavitary (e.g., hemoabdomen, hemothorax), or into tissues (e.g., pulmonary contusions, crushing injuries). Primary intervention goals in these patients are to attenuate any ongoing bleeding not stopped by endogenous hemostasis (7, 8), appropriate and judicious volume expansion (based on patient's clinical response to volume of blood lost) and appropriately monitoring for development of consumptive coagulopathy and addressing co-morbidities associated with extravasation of blood (e.g., pulmonary contusions, cerebral hemorrhage).

Traumatic Injury Causing Blood Loss, Coagulopathic

Trauma Induced Coagulopathy (TIC) is defined as the culmination of endogenous responses to hemorrhagic shock plus tissue injury (3). At presentation, TIC clinically manifests in a spectrum of phenotypes from hypocoagulable to hypercoagulable that impact decisions regarding appropriate initial intervention (3, 9–11). Individual patient's coagulopathic status can be dynamic throughout the resuscitation and resolution period as a result of ongoing blood loss, degree of endothelial injury, and interventions selected by the clinician. In these patients, primary intervention goals include those listed for non-coagulopathic traumatic bleeding, in addition to interventions based on diagnostic results (e.g., viscoelastic coagulation monitoring or specific hemostatic parameter measurement) and resources (e.g., whole blood, autotransfusion, component therapy) available to the clinician.

Non-traumatic Spontaneous Bleeding, Non-coagulopathic

These are patients that are experiencing blood loss as a result of vascular defects caused by neoplasia (e.g., splenic hemangiosarcoma) or underlying disease (e.g., gastric ulcer, mast cell tumor). During primary survey, these patients can be a bit more challenging to identify as hemorrhagic shock until initial diagnostics are obtained. As such, in a patient showing signs of hypovolemic shock at presentation, initial intervention is typically volume expansion while preliminary diagnostics are performed to determine cause. If present, once shock is identified as hemorrhagic, intervention goals are similar to that of traumatic injury non-coagulopathic patients.

Non-traumatic Spontaneous Bleeding, Coagulopathic

Similar to TIC, these are patients that have progressed to coagulopathy as a result of blood loss (without concurrent tissue injury). However, in contrast to TIC, these patients are identified as being in Disseminated Intravascular Coagulopathy (DIC) as a result of the consumptive processes associated with endogenous hemostatic efforts plus or minus contributions of endothelial damage due to underlying disease (12). Similar to non-coagulopathic, non-traumatic spontaneous hemorrhage, early identification of hemorrhage and source of bleeding are key. As with TIC, stabilization interventions are ideally based on diagnostic results (e.g., viscoelastic or specific hemostatic parameter monitoring) and resources (e.g., whole blood, autotransfusion, component therapy) available to the clinician.

Primary Hemostatic Disorder

These are patients that are bleeding spontaneously from normal vascular "wear and tear" and have an inadequate ability for the endogenous hemostatic system to stop bleeding. Examples include thrombocytopenia (e.g., Immune-mediated thrombocytopenia, Ehrlichia), thrombocytopathia (e.g., Von Willebrand's Disease, medications), clotting factor deficiencies (e.g., hemophilias), or inactivity (e.g., anti-coagulant rodenticide). Primary intervention goals in these patients are to attenuate any ongoing bleeding which may require supplementation of endogenous hemostatic components that are deficient (e.g., platelets, plasma, cryoprecipitate), and based on patient's clinical status and degree of blood loss (**Table 2**), appropriate restoration of adequate oxygen delivery. An additional goal is to identify and administer therapies for those hemostatic defects that have a specific intervention that is able to prevent further bleeding (e.g., Vitamin K1 in anti-coagulant rodenticide toxicity).

TABLE 1 | Considerations for various manifestations of acute blood loss resulting in hemorrhagic shock.

	Anatomic considerations for investigating blood loss	Clinicopathological parameters	Common manifestations	Approach
Traumatic injury *Non-coagulopathic	External blood loss (e.g., oral, facial or skin wounds or lacerations) Internal blood loss - Gastrointestinal - Abdomen - Retroperitoneum - Thorax - Pericardium - Within solid organs (e.g., muscle, lung)	Packed cell volume increased (dogs), normal, decreased depending upon acuity a degree of hemorrhage Total protein/total solids: normal or decreased Lactate: increased (more likely in dogs than cats) BE: greater negative base excess paralleling lactate changes Decreased central venous oxygen saturation depending on severity PT/PTT: normal Platelets: normal to decreased	Blunt trauma (e.g., hit by vehicle, fall from height) Penetrating trauma (e.g., bite wounds, missiles)	Attenuate blood loss Crystalloids to ensure tissue perfusion with minimize dilutional and endothelial damage effects Ideal: replaced blood loss using PBC/Plasma/platelets in appropriate ratio or use fresh whole blood to replace? Colloids if low volume crystalloids ineffectual and blood product not available Active rewarming for patients without traumatic brain injury
Traumatic injury *Coagulopathic		Same as above except prolonged coagulation and/or abnormal viscoelastic monitoring parameters		Same as above. Correct acidosis with improving perfusion Active rewarming even more important Tranexamic acid?
Spontaneous bleeding (Non-traumatic) *Non-coagulopathic		Same as Traumatic injury non-coagulopathic	Splenic mass (e.g., hemangiosarcoma) Gastric ulceration Skin mast cell tumors	Same as trauma induced non-coagulopathic
Spontaneous bleeding (Non-traumatic) *Coagulopathic		Same as above Traumatic coagulopathic		Same as Trauma coagulopathic Vitamin K if rodenticide
Primary hemostatic disorder		Varies depending on underlying mechanism	Anticoagulant rodenticide (ACR) toxicity Immune-mediated thrombocytopenia Thrombocytopathias	Same as any blood loss hypovolemia Appropriate reversal or support of deficiencies, for example: Vitamin K (ACR) Platelets concentrates Treat Platelet dysfunction as indicated

PHYSIOLOGIC AND PATHOPHYSIOLOGIC CONSIDERATIONS

In the continuum of advancing clinical care from bench to bedside, mechanistic models serve to describe the biological processes and physiology of a disease and/or the mechanism of action of an intervention. Utilization of the dog in preclinical and mechanistic models of hemorrhage is uncommon, but a number of published studies do exist (13–20). Model designs vary from fixed volume studies (removal of a set quantity of blood) to fixed pressure studies (removal of a quantity of blood to a set blood pressure). Other model variations include timing of hemorrhage, anesthetic protocol, addition of tissue injury, timing to intervention and type of intervention(s). These variations make broad generalizations across studies difficult. Despite differences in study design, in the hemorrhage phase of all studies, documented changes in instrumented, clinical and biochemical parameters have similar trends.

Hemodynamic Changes Observed in Hemorrhagic Shock

The physiologic dose and response to whole blood loss in the canine patient is repeatable both in anesthetized (13–20) and awake animals (21). In addition to clinical and biochemical variables, these well-instrumented models measure cardiac index, central venous pressure, systemic vascular resistance, oxygen extraction ratios, oxygen delivery, and oxygen content. As progressive blood volume and oxygen carrying capacity from the intravascular space is lost, compensatory mechanisms come into play to attempt to maintain adequate delivery of oxygen to tissues (**Figure 1**). Decreased cardiac output due to decreased stroke volume (volume loss) is countered by activation of the renin-angiotensin-aldosterone-system (RAAS) and sympathetic nervous system leading to increased heart rate, contractility and systemic vascular resistance.

Decreased arterial oxygen content resulting from loss of hemoglobin is countered by mobilization of abdominal organ blood reserves into splanchnic circulation. In both dogs and

TABLE 2 | Signs and symptoms of hemorrhage by class as defined in the American college of surgeons advanced trauma life support 10th edition manual.

Parameter	Class I	Class II (mild)	Class III (moderate)	Class IV (severe)
Approximate blood loss	<15%	15–30%	31–40%	>40%
Heart rate	↔	↔ / ↑	↑	↑ / ↑↑
Blood pressure	↔	↔	↔ / ↓	↓
Pulse pressure	↔	↓	↓	↓
Respiratory rate	↔	↔	↔ / ↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit*	0 to −2 mEq/L	−2 to −6 mEq/L	−6 to −10 mEq/L	−10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive transfusion protocol

**Base excess is the quantity of base (HCO_3^-, in mEq/L) that is above or below the normal range in the body. A negative number is called a base deficit and indicates metabolic acidosis.*
↔Little to no change.
↓Decreased.
↑Increased.
Reprinted with permission from American College of Surgeons ATLS 10th Edition manual, Tables 3-1.

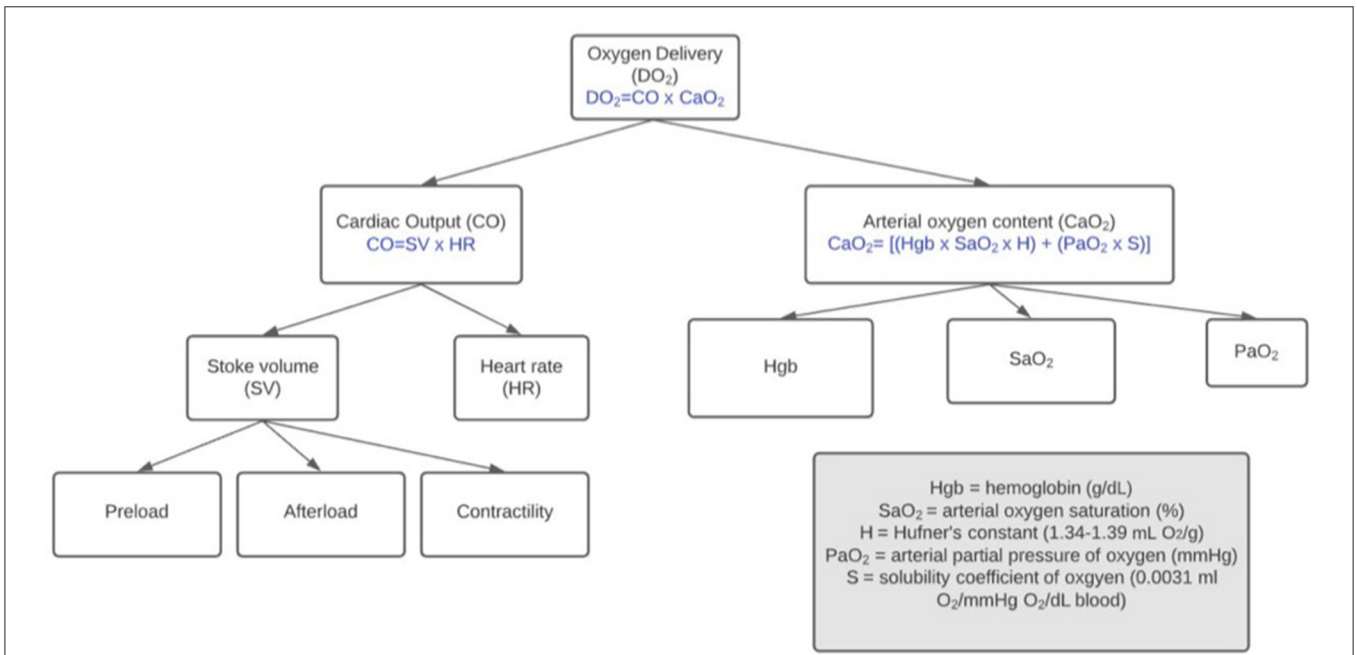

FIGURE 1 | Factors affecting delivery of oxygen to tissues. During hemorrhagic shock (decreased DO_2), the patient's physiologic compensatory mechanisms and clinician's intervention strategy relationships are interrelated.

cats, splanchnic circulation contributions to counteract blood volume loss is similar in total (∼4.9 ml/kg cat; ∼5.1 ml/kg dog). In dogs, splenic contraction is the biggest contributor whereas in cats, the contributions from liver, intestine and spleen are similar (14). In splenectomized dogs, a significant decrease in hemoglobin after acute hypotensive hemorrhage occurs; however, decreases in hemoglobin concentration do not occur in hemorrhaged dogs with an intact spleen (22, 23). In dogs, splenic contraction launches a significant number of red blood cells into the circulation. The net effect is a lesser impact of changes in hemoglobin concentration and oxygen carrying capacity compared to pre-hemorrhage levels in the pre-resuscitation phase of bleeding. Because arterial oxygen content may be less significantly impacted during acute hemorrhagic states, in dogs, the decrease in oxygen delivery is mainly attributable to a decrease in cardiac output (**Figure 1**).

Other systemic consequences and effects are dependent on the proportion of volume lost, duration of ongoing bleeding, and individual patient factors regarding compensatory reserve (**Table 2**). While impacted by the rate of loss, in dogs, cardiac arrest occurs when ∼60–90% of blood is lost (24, 25) or mean arterial pressure (MAP) falls below 30–40 mmHg (13).

Clinical Parameters (HR, SBP)

While an increase in heart rate (HR) and decrease in systolic blood pressure (SBP) are noted in canine models of hemorrhagic shock, compensatory mechanisms may result in these values remaining in the clinically normal reference interval until ∼15–20% of total blood volume is lost (19). However, their relationship as represented by shock index (SI = heart rate/systolic blood pressure) may be an early indicator of compensatory shock, and requirement for volume resuscitation. Clinical literature and pre-clinical literature suggest that a SI > 1.0 at presentation warrants further investigation of volume loss and appropriate intervention (19, 26–28).

Biochemical Parameters (pH, Lactate, Bicarbonate, Base Excess, Hemoglobin)

As blood volume is lost, compensatory mechanisms including buffering systems and ventilation adjust in an effort to maintain normal blood pH in the face of systemic metabolic acidosis characterized by significantly lower base excess and increases in lactate. The acidosis associated with acute hemorrhage can compound coagulopathy and result in continued bleeding (29). Volume resuscitation efforts to return appropriate delivery of oxygen and nutrients to tissues is key, and serial evaluation of base excess and lactate can help inform intervention decisions (16, 30, 31). While reduction in hemoglobin (Hgb) is noted with severe to catastrophic bleeding, with mild to moderate hemorrhage, prior to resuscitation, Hgb may be in the normal reference range. Clinically, normal Hgb at presentation does not rule out acute hemorrhage, and serial evaluation during volume resuscitation phase is useful.

Coagulation

Hemostatic abnormalities are a major factor in the treatment of acutely bleeding patients, both in traumatic and non-traumatic hemorrhage. While there was a period of research that suggested that acute large volume hemorrhage in trauma was primarily associated with hypocoagulability and hyperfibrinolysis, growing evidence supports a continuum dependent on not only duration, amount of blood loss and clinician interventions, but also patient factors (**Figure 2**). This spectrum of hemostatic dysfunction is evident in pre-clinical canine hemorrhage research (33) as well as canine trauma clinical research (9–11, 34). In trauma patients, the added component of tissue injury, on top of blood loss, further clouds the picture, leading to various clinical manifestations of trauma induced coagulopathy (**Figure 2**). The body of evidence in human patient care regarding a spectrum of phenotypes associated with acute traumatic hemorrhage is growing (3). The advancement and development of bedside global hemostatic and fibrinolytic testing is enabling the ability to use blood product and resuscitation strategies based on individual patient parameters.

Endothelium and Glycocalyx

Knowledge regarding the contributions of the endothelium and glycocalyx in injury and resuscitation is expanding rapidly (31, 32, 35, 36) (**Figure 2**). Mechanistic and clinical research to better describe the physiology and systemic response are expanding rapidly. As a result, there is clinical equipoise regarding "first choice" of volume resuscitation fluid for the acutely hemorrhaging patient in both human and veterinary medicine. Regarding the endothelium specifically, while no fluid is risk-free, there is evidence that crystalloid resuscitation may exacerbate endothelial and glycocalyx dysfunction and synthetic colloids are under continual review of their risks and benefits in hemorrhagic shock resuscitation (17, 33, 37) (*Cross reference Frontier articles: "The effects of resuscitative fluid therapy on the endothelial surface layer," Smart/Hughes AND "Article 7 Colloids, Yes or No? Pros and Cons of Colloids?" (Adamik/Yosova)*. Large clinical trials evaluating alternative initial resuscitation fluid based on severity of disease and time to definitive care are underway in human medicine (38–41).

There is a broad range of clinical presentations of the acutely hemorrhaging veterinary patient as noted in section Definition of Problem and Causes. Understanding the physiology and mechanisms associated with acute blood loss help inform both clinical assessment and intervention decisions. In addition to patient variables (amount of blood lost, co-morbidities, hemostatic ability, compensatory reserve), resources available to the practitioner and pet owner influence the clinical approach to the acutely hemorrhaging veterinary patient. Despite a varied range of manifestations of the acutely hemorrhaging patient, a systemic approach as outlined below is recommended.

APPROACHES TO FLUID RESUSCITATION IN THE MEDICAL FIELD

There has been a substantial change in human medicine regarding resuscitation for hemorrhagic shock from massive fluid administration to minimal fluid resuscitation while maintaining permissive hypotension and utilization of transfusion with a balanced ratio of blood products and goal directed correction of coagulopathy (3, 4). In some human hemorrhaging patient populations, plasma has replaced crystalloids for volume expansion (38–40).

For years, aggressive crystalloid therapy was utilized to treat hemorrhage shock. In fact, Shoemaker et al. recommended supra-normal resuscitation with crystalloids during shock. He found that this mode resulted in increased oxygen delivery to tissues and improved survival in critically ill patients (42). Unfortunately, this aggressive therapy resulted in generalized tissue edema, particularly bowel edema resulting inability to close the abdominal wall (43). Later, researchers demonstrated an association between supra-normal resuscitation and increased incidence of abdominal compartment syndrome, multiple organ failure, and decrease survival (44). Closer investigation into the consequences of supranormal resuscitation found compromised cellular function causing alterations in glucose metabolism and cardiac myocyte excitability (45–48). Subsequent studies have shown that aggressive crystalloid resuscitation can cause dilutional coagulopathy, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), hypoxemia, compartment syndrome, endotheliopathy, and greater mortality (49, 50). Finally, subsequent randomized

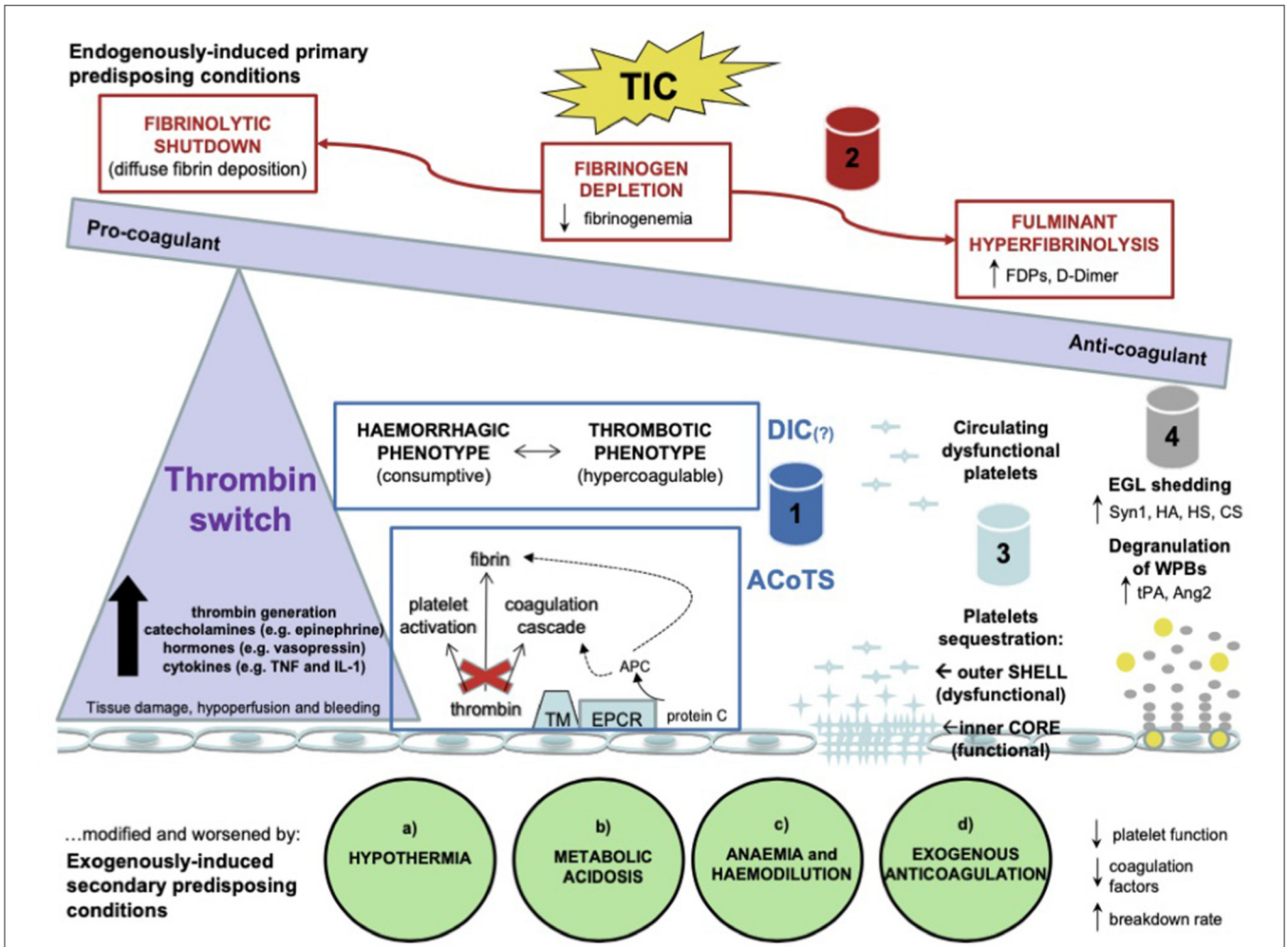

FIGURE 2 | A schematic representation of the pathophysiological alterations in the hemostatic system occurring after trauma. Tissue damage, hypoperfusion and massive bleeding are the main drivers of the inflammatory and neurohormonal response with a significant increase in thrombin generation, catecholamines, hormones, and cytokines. Thrombin undergoes a systemic release which determines the so called "thrombin switch" toward anticoagulation. Trauma induced coagulopathy (TIC) is considered as a series of endogenously induced primary predisposing conditions based on 4 pillars: 1–endogenous anticoagulation in the form of disseminated intravascular coagulation (DIC) or acute coagulopathy induced by trauma and shock (ACoTS); 2–fibrinogen depletion, hyperfibrinolysis and fibrinolytic shutdown; 3–platelet dysfunction; 4–endotheliopathy. These conditions can be modified and worsened by exogenously induced secondary predisposing conditions in the presence of (a) hypothermia, (b) metabolic acidosis, (c) anemia and hemodilution, (d) exogenous anticoagulation. DIC, disseminated intravascular coagulation; ACoTS, acute coagulopathy induced by trauma and shock; FDPs, fibrinogen degradation products; TM, thrombomodulin; EPCR, endothelial protein C receptor; APC, activated protein C; EGL, endothelial glycocalyx layer; Syn1, syndecan-1; HA, hyaluronic acid; HS, heparan sulfate; CS, condroitin sulfate; WPBs, Weibel-Palade bodies; tPA, tissue plasminogen activator; Ang2, angiopoietin-2; PAR1, protease activated receptor 1; TM, thrombomodulin; APC, activated protein C; NO, nitric oxide; PGI_2, prostaglandin I_2; tPA, tissue plasminogen activator. Reprinted by permission from Springer Nature: Internal and Emergency Medicine, The current understanding of trauma-induced coagulopathy (TIC): a focused review on pathophysiology. Giordano et al. (32).

control studies utilizing supra-normal resuscitation did not demonstrate Shoemaker's initial successes (51).

Hypertonic saline is an attractive low volume resuscitation crystalloid. Its benefits include rapid increases in cardiac output and blood pressure (52), improved microcirculatory flow through decreasing endothelial edema (53), and combating inflammation through suppression of pro-inflammatory mediators and increased anti-inflammatory mediators (54, 55). Despite these favorable attributes, a multicenter randomized control study on hemorrhagic shock comparing normal saline, hypertonic saline, and hypertonic saline dextran did not show any difference in survival (56). Subsequent to this study, interests in hypertonic saline in prehospital resuscitation of hemorrhagic shock has decreased as evidence for more favorable outcomes using plasma for volume replacement has become evident.

Synthetic colloids such as hydroxyethyl starch (HES) have historically been used as a resuscitative fluid in hemorrhagic shock patients in veterinary medicine due to their rapid volume expansion, availability and cost (57, 58). Recent evaluation of their effects on coagulation in canine hemorrhage models (33) and attenuation of their use in human clinical medicine has impacted veterinary utilization (*cross reference Frontiers article:*

Colloids…"Article 7 Colloids, Yes or No? Pros and Cons of Colloids?" (Adamik/Yosova)).

Permissive Hypotension

Similar to the philosophical approach to damage control surgery (DCS) where there is an attempt to stop or minimize hemorrhage as soon as possible in the surgical suite, anecdotal clinical observations of increasing blood pressure with fluid resuscitation may create vascular pressure exacerbated bleeding. To this end, studies were developed to investigate the effects of minimizing increases in blood pressure to allow for vital organ perfusion but limited excessive pressures beyond that. Many of the initial studies were conducted in animal models and a summary of the results was published in a meta-analysis of these studies (59). All resulted in decreased mortality compared to normotensive fluid resuscitation. Taking these results to the human field, the results have been less conclusive. One study compared normal pre-hospital fluid resuscitation to delaying fluid resuscitation in penetrating torso patients until arrival in the trauma operating room. They found improved survival in the latter group (70 vs. 62%) (60). Another study compared high blood pressure (systolic: 100 mmHg) to low blood pressure (systolic: 70 mmHg) endpoints and there was no difference in mortality (61). A subsequent study with similar systolic pressure endpoints reported improved survival in blunt trauma patients but not in penetrating trauma patients (62).

There is not strong evidence to support an ideal pressure goal with hypotensive resuscitation and how long it can be maintained. In addition, most of these studies have used crystalloid solutions as part of their resuscitation and there have been no definitive studies using hypotensive resuscitation with blood component therapy. None of the studies cited above were performed in patients with head trauma and hypotensive resuscitation in patients with head trauma and increased intracranial pressure is not recommended (63, 64).

Component Therapy

Early studies on animal blood transfusion demonstrated the effectiveness of whole blood transfusion on resuscitation in hemorrhagic shock but it was fraught with infections, clotting and other complications. With refinement in collection techniques and anti-coagulants, these hurdles were overcome and whole blood transfusion became a useful therapy in hemorrhagic shock. The scarcity of blood products eventually led to the more efficient use of component therapy.

Early standard resuscitation component therapy included sequential resuscitation with crystalloids, artificial colloids, and packed red blood cells (65). With the advent of Damage Control Resuscitation (DCR), this type of component therapy began to evolve to an increasing plasma to packed red blood cell (pRBC) ratio. A study performed during the Iraq War investigated the use of three different patient cohorts based on ratios of plasma:pRBC including a low ratio (1:8), a medium ratio (1:2.5) and a high ratio (1:1.4) (66). The all-cause mortality and death from hemorrhage rates both decreased in the low ratio cohort when compared to the other two cohorts. Similar findings were demonstrated in people with ruptured aortic aneurysm using historical controls (67). Another observational study in civilian trauma patients showed similar findings with early resuscitation with higher ratios of plasma and platelets to pRBCs (68). More evidence supporting higher ratios of plasma and platelets was demonstrated in a prospective, randomized clinical trial in bleeding trauma patients comparing 1:1:1 to 1:1:2 plasma to platelet to pRBCs (69). Although no difference in 24-h or 30-day survival was noted, the lower ratio group was more likely to achieve hemostasis and had decreased death due to hemorrhage. These studies and others have led to the recommendations using higher plasma to pRBC ratios during massive transfusion ($>$ 10 units of packed red blood cells within a 24 h period or $>$ 5 units within 4 h). In fact, in the American College of Surgeons Trauma Quality Improvement Program Massive Transfusion in Trauma Guidelines, developed by a panel of expert trauma surgeons, recommend to begin resuscitation with blood component therapy (rather than using crystalloids or colloids) with a plasma to pRBC ratio ranging from 1:1 to 1:2 ratio (70).

The underlying benefits using component therapy compared to crystalloid resuscitation are not completely elucidated but several reported advantages include but are not limited to mitigation of hyperfibrinolysis and platelet function and repair of endothelial integrity (71, 72). In veterinary medicine, utilization of (fresh) frozen plasma and stored pRBCs, in a 1:1 or 1:2 ratio is feasible.

Platelets

Given the improvement in outcomes using plasma and blood component therapy studies have been performed to investigate the use of platelets in blood component therapy. Similar to plasma, high ratios of platelet concentrates to pRBC have demonstrated decreased risk of death in massively transfused patients (68, 73, 74). The American College of Surgeons Committee on Trauma recommends transfusing one unit of platelets to every 6 units of pRBCs (70).

Fresh Whole Blood

Given the success of component therapy, why not just use fresh whole blood? The use of fresh whole blood in war casualties has an extensive history particularly from the conflicts in Afghanistan and Iraq (4). Studies during these conflicts found improved survival in patients that received fresh whole blood compared to plasma and pRBC component therapy. A particular advantage of fresh whole blood is that it does not require drawing multiple component units and provides balanced components in one administration. There are many hurdles to the use of fresh whole blood including access, the short shelf life of "fresh whole blood" and rapid screening for infectious disease (unless donor present has already been screened) (75–77).

The Veterinary Caveat

Component therapy has become the preferred method in resuscitation of severe hemorrhage in humans but there are hurdles to the use of it in veterinary medicine. Many of the

studies cited in this section above indicated that this therapy is most effective within the first few hours of hemorrhage and its effect on outcome diminishes after this period. Anecdotally, it is recognized that the speed with which hemorrhaging veterinary patients are taken to surgery for definitive hemorrhage control is much more delayed compared to human medicine (with some exceptions). This delay may negate the positive results with component therapy. Similarly, component therapy may not be readily available to the many veterinary hospitals. Additionally, plasma concentrates are also not consistently available. While there remains much to learn in clinical veterinary patients, experimental studies in animals show that replacement of lost blood, sometimes as components, administered early has improved outcomes (18, 20, 23).

CURRENT RECOMMENDATIONS

Consensus on the best approach to volume resuscitation in the acutely hemorrhaging patient does not exist in veterinary medicine due to multiple factors including, but not limited to, lack of prospective clinical trials, limited similarly designed projects amenable to meta-analyses, and challenges extrapolating human and pre-clinical model findings to clinical canine and feline patients with similar, but not identical, physiologic responses to hemorrhage and resuscitation. However, this challenge is not unique to veterinary medicine, and continued research efforts to individualize resuscitation in the hemorrhaging patient based on patient phenotype, response to interventions, degree of disease and environment remain a significant pursuit (3, 12, 78). In the meantime, clinicians are left to make decisions for patients daily based on interpretation of the research that exists. The following recommendations regarding the approach to the acutely hemorrhaging canine or feline trauma patient relies heavily on the authors' interpretation of preclinical, mechanistic and limited veterinary clinical studies reviewed in the references. The algorithm presented here for veterinary patients was inspired by and adapted from a similar algorithm developed by the ATOMAC group regarding non-operative management of blunt liver and spleen injury in children (79). The authors put this forth as a current recommended guideline, and anticipate generation of a similar guideline in the near future as veterinary groups begin developing clinical practice guidelines based using GRADE methodology. Evidence to support best practices for volume resuscitation in the hemorrhaging cat is sparse, and efforts to acknowledge differences are made.

Initial triage of the acutely ill patient has many approaches with different assessment algorithms taught and applied. The British military has added Catastrophic bleeding (<C>) to the American College of Surgeons Airway (A), Breathing (B), Circulation (C), Disability (D), Environment/Exposure (E) approach to the primary survey of the acutely injured patient methodology that it advocates utilizing (80). Regardless of approach, patients with circulatory shock associated with blood loss require immediate intravascular access and interventions to ensure adequate delivery of oxygen to tissues. While determination of an underlying cause is important, respiratory, cardiovascular, and neurologic stabilization should be prioritized and initiated immediately.

During the intravascular resuscitation phase of the acutely hemorrhaging patient, reassessment parameters include physical exam findings (temperature, respiratory rate and effort, pulse rate and quality, mucous membrane color, capillary refill time, and mentation), biochemical measurements [packed cell volume or hemoglobin, total protein/solids, base excess (deficit), lactate and pH], and macro-perfusion measurements (blood pressure). Once circulatory stabilization is underway, continued determination of underlying cause (**Table 1**) and consequences to determine further intervention is required. If perfusion parameters from physical exam, biochemical measurements, or macro-perfusion measurements worsen during resuscitation, reassessment of the primary survey is initiated, and interventions selected based on patient findings and patient status at that point (**Figure 3**).

While there continues to be a shift in first choice resuscitation in the recently hemorrhaged patient in shock, current literature (and logistics) supports a 10–20 ml/kg dog (5–10 ml/kg cat) intravascular dose of a balanced electrolyte solution (LRS, Plasma-lyte 148, Normosol-R). In the subset of hemorrhaging patient's whose clinical status has not stabilized, the clinician's choices from there vary based on patient status, response to interventions and blood product availability. Consideration for blood product administration in the poorly responding hemorrhaging patient early in resuscitation is recommended (**Figure 3**).

A series of veterinary papers evaluating various triage values and subsequent blood transfusion in canine trauma patients found an association between abdominal fluid score (AFS), base excess (BE) and ionized calcium (iCa), respectively, as independent predictors of patients receiving a blood transfusion. These findings suggest consideration for readying blood product for administration when initial triage diagnostics include an AFS $\geq$ 3, BE $<$ −6.6 mmol/L, and ionized iCa $<$ 1.24 mmol/L or $<$ 2.50 mEq/L (30, 81, 82). Given the logistics required to warm (pRBCs) and/or thaw (FFP), when these parameters are identified, the recommendation is to considering beginning that process.

Veterinary and human literature demonstrate a spectrum of coagulation and fibrinolytic abnormalities in acutely hemorrhaging patients (3, 9–11, 34). In human medicine, antifibrinolytic agents have been studied and utilized in various clinical scenarios that result in hemorrhage, including trauma, postpartum and orthopedic surgery patients (83). The CRASH-2 trial demonstrated improved survival in acutely hemorrhaging trauma patients when tranexamic acid (TXA) is administered within 3 h of injury (84). In veterinary medicine, there is evidence that dogs are more hyperfibrinolytic when compared to humans (85). While numerous studies support the effectiveness of TXA in blunting hyperfibrinolysis in dogs (86, 87), unless viscoelastic testing evidence of hyperfinbrinolysis resulting in ongoing bleeding is evident, its "standard use" in all hemorrhaging patients has not yet been established (88). That said, given limited availability to universally available viscoelastic testing in veterinary medicine, in an acutely hemorrhaging canine patient not responding to hemorrhage control and volume resuscitation,

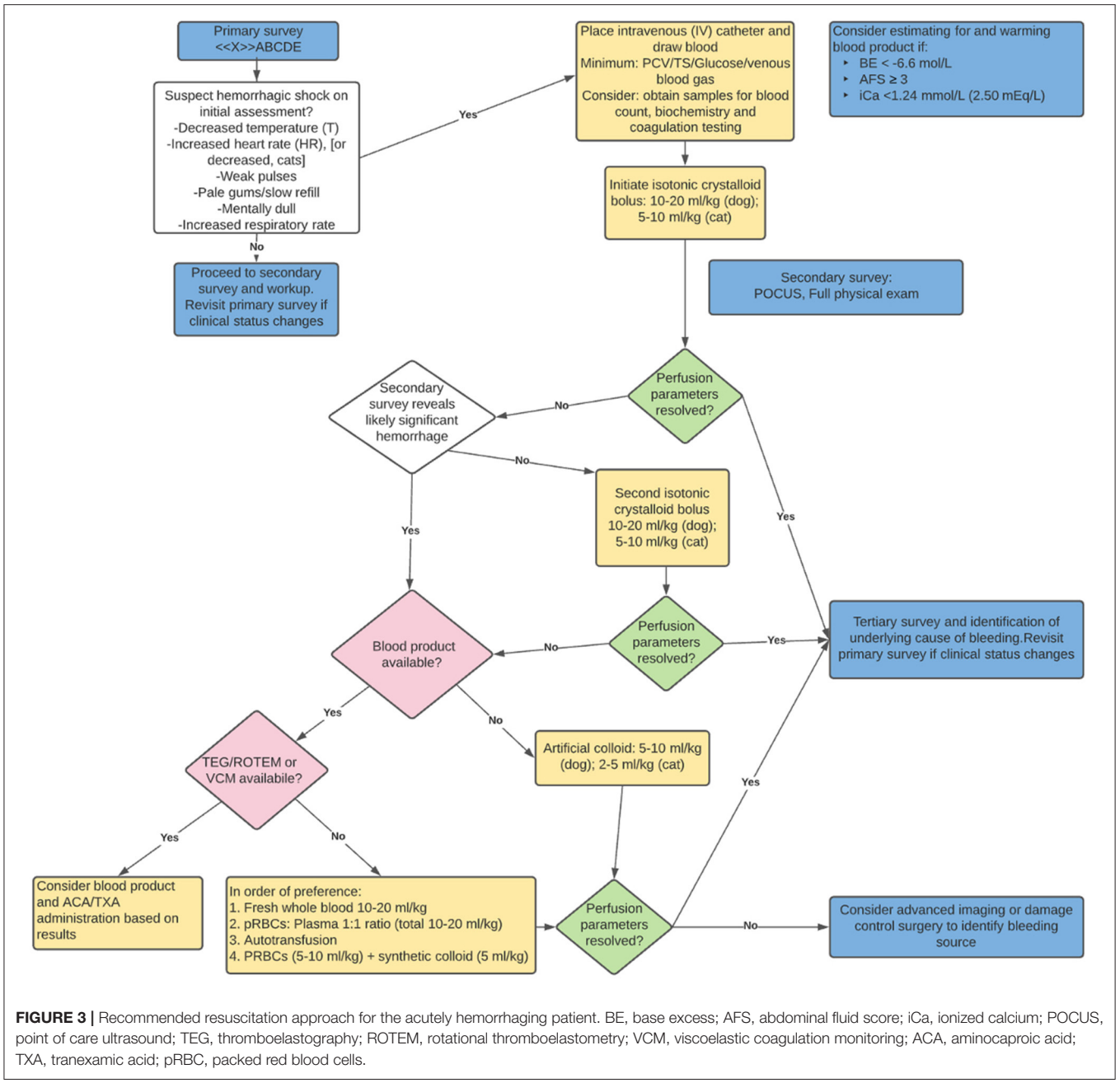

FIGURE 3 | Recommended resuscitation approach for the acutely hemorrhaging patient. BE, base excess; AFS, abdominal fluid score; iCa, ionized calcium; POCUS, point of care ultrasound; TEG, thromboelastography; ROTEM, rotational thromboelastometry; VCM, viscoelastic coagulation monitoring; ACA, aminocaproic acid; TXA, tranexamic acid; pRBC, packed red blood cells.

it is reasonable to consider the use of antifibrinolytics (TXA or Aminocaproic acid). While the literature is sparse, cats may be at more risk for developing comorbidities with administration of TXA (89). Additionally, there is risk of hypercoagulability and thromboembolic events in cats after trauma (90). The routine utilization of antifibrinolytics in hemorrhaging cats is not recommended based on current literature.

In summary, current evidence supports judicious use of a balanced electrolyte solution, and early movement to "replacing what is lost" in the acutely hemorrhaging patient by utilization of blood product, when available (**Figure 3**). Future developments in lyophilized or other "long shelf life" component therapy may help bridge the gaps in cost, access and availability of blood product in veterinary medicine, and if research supports their effectiveness, may expand veterinarian's ability to address the hemorrhaging patient more universally.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Traumatic Brain Injury—A Review of Intravenous Fluid Therapy

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This manuscript will review intravenous fluid therapy in traumatic brain injury. Both human and animal literature will be included. Basic treatment recommendations will also be discussed.

Keywords: traumatic brain injury, TBI, fluid therapies, colloid, crystalloid, osmotherapy, mannitol, hypertonic saline

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INTRODUCTION

It is reported that up to 34% of dogs and cats sustaining blunt force trauma will have head and neck injury. In 10% with mild head injury and 80% with severe head injury, intraparenchymal and extra axial hematomas have been detected with advanced imaging (1). Evidence of head trauma is significantly associated with mortality in dogs suffering blunt force trauma (2) and the overall mortality rate is reported to be 24–35% (3, 4). Therapeutic interventions for treating dogs and cats with traumatic brain injury (TBI) are extrapolated from experimental evidence, isolated veterinary reports, human clinical investigations, and anecdotal experience. Confounding injuries, including hemorrhage and additional organ injury, can complicate the decision-making process as well as outcome. Understanding the unique anatomy of the blood brain barrier (BBB) and autoregulation of blood flow, and how they become affected by trauma can provide the clinician with a foundation from which to write a fluid prescription for the patient with TBI.

NORMAL BLOOD BRAIN BARRIER

The brain is highly dependent on a continuous and regulated supply of oxygenated blood traveling through a highly regulated conduit lined by the BBB. The BBB is a physical, transport, and metabolic wall that separates the contents of the blood vessels from the brain interstitium and cells. The endothelial cells lining the vessels of the brain are fenestrated by transmembrane proteins (occludin and claudins or junctional adhesion molecules) anchored to the cytoplasmic surface by scaffolding proteins (zonula occludens) that physically control particle movement through the intercellular clefts and paracellular pathways (5). The capillary membrane is incompletely swathed by pericytes, and together they are encased by a basement membrane constructed by extracellular matrix molecules. Astrocytes extend cellular processes that encase the vessel, neuronal synapses, and nodes of Ranvier, which together make the neurovascular unit. Specific transport mechanisms mediate solute movement across the BBB, and enzymes metabolizing molecules in transit act as a metabolic barrier.

An intact BBB acts as a solute exchange barrier between circulating blood and the brain environment, and functions to allow nutrient delivery and waste removal while limiting entry of immune cells, pathogens, and toxins. The intact BBB is permeable to oxygen, water, and small lipid soluble molecules.

BLOOD BRAIN BARRIER DISRUPTION IN TRAUMATIC BRAIN INJURY

Dysfunction of the BBB precipitates several key events (6). Paracellular transport of restricted components, in particular neutrophils, increases with the loss of tight junction proteins, and transcytosis of larger molecules such as serum proteins increases across the endothelial cell. This establishes an inflammatory response and an increase in interstitial fluid resulting in vasogenic edema. In addition, activation of cellular membrane ion channels results in intracellular water accumulation and cytotoxic edema, culminating in an increase in brain volume. Following a traumatic event, brain edema will be heterogenous, and alterations in blood flow and oxygen delivery will depend on the severity and region(s) affected.

Since the brain parenchyma is protected within a non-distensible calvarium, an increase in brain volume from edema will increase ICP and reduce CPP in a non-linear manner, resulting in brain ischemia, the single most important secondary insult that can occur following TBI. Therapeutic goals in mitigating the reduction in CPP include optimizing systemic MAP, and, when necessary, decreasing intracranial volume with osmotherapy.

CPP AND OPTIMIZING MAP

Blood flow to the normal brain is minimally affected with a MAP between 50–150 mmHg due to autoregulatory mechanisms. A traumatic insult to the brain is followed by disruption of the BBB and cellular injury, and infiltration of inflammatory cells. Their release of cytokines induces nitric oxide production resulting in vasodilation and failure of cerebral pressure autoregulation. Cerebral blood flow in the injured region then becomes dependent on CPP. Systemic hypotension becomes a major contributor to a reduction in CPP, and therefore must be corrected and prevented. Causes of hypotension in patients with TBI can include hemorrhage, third-space fluid losses, and vasoplegia. In addition, polytrauma is common in patients with TBI, and multiorgan damage resulting in hypoxemia, hypovolemia, and systemic inflammation can contribute to the secondary insult to injured brain tissue and complicate the approach to treatment.

Intravenous (IV) fluid therapy is the mainstay of fluid resuscitation from hypovolemia regardless of the extent of trauma. Fluid types include a balanced, buffered, isotonic crystalloid (e.g., Plasma-Lyte, Normosol-R), an isotonic crystalloid with a higher sodium concentration (0.9% sodium chloride), hypertonic saline (HTS 3–7.5%), and/or a synthetic or natural colloid. It can be argued that hyponatremic fluids [e.g., lactated Ringer's solution (LRS)] should be avoided unless the patient is hyponatremic, since they might produce an increased osmolar gap that could favor brain water accumulation (7). A discussion on studies relevant to fluid therapy in animals and people with TBI follows.

RESUSCITATION FLUIDS IN PATIENTS WITH TRAUMATIC BRAIN INJURY AND HEMORRHAGIC SHOCK

Widely recognized for their guidelines for treating TBI, the Brain Trauma Foundation (BTF) (8) and the Lund Concept (9) have published controversial recommendations for the treatment of TBI. The BTF interventions are based on a set of evidence-based recommendations gleaned from a literature review of published studies, and the BTF guidelines do not make any recommendations about the use of any specific fluid type. The Lund Concept describes non-individualized, pre-emptive, ICP-regulating and perfusion-targeted therapy for manipulating transcapillary fluid dynamics using albumin (in addition to vasodilators and avoiding the use of vasopressors), but lacks strong evidence supporting the protocol (10, 11). There are no clinical trials evaluating any fluid type for resuscitation from hemorrhagic shock in veterinary patients with TBI. There are however dog, cat, pig, rat, and mouse models of hemorrhagic shock and TBI that have been used in the laboratory setting, as well as human clinical trials, attempting to identify the optimal fluid for resuscitation.

Isotonic Crystalloids

Isotonic crystalloid solutions have been evaluated in the laboratory and human clinical trial setting. They are often the first-line therapy in the pre-hospital environment. However, crystalloids lack any pro-survival properties (12) and there is no survival benefit associated with aggressive crystalloid resuscitation in bleeding patients (13, 14). Modern damage control resuscitation guidelines for hemorrhaging patients recommend avoidance of crystalloid fluids in favor of early initiation of a 1:1:1 ratio-based transfusion strategy using packed red blood cells, plasma, and platelets (15). This strategy may mitigate hemodilution, hemostatic derangements, brain edema, and inflammation associated with large volume crystalloid infusion and worsening of uncontrolled hemorrhage (9, 15–17). In a pig model of TBI and uncontrolled hemorrhage, 100% of pigs died in less than one hour when aggressively resuscitated with isotonic crystalloid solution to a MAP of 80 mmHg, while 50% of pigs that were allowed to remain hypotensive with no resuscitation for one hour survived and went on to have cerebral blood flow return to normal in the second hour following surgical hemostasis and resuscitation with shed blood (18). Hypotensive resuscitation during damage control resuscitation is contraindicated in people with TBI, where resuscitation to a systolic BP of 90–110 mmHg with limited crystalloid infusion is recommended (15).

When compared to synthetic colloids, animals resuscitated with 0.9% sodium chloride or LRS required larger volumes of fluid to reach and maintain hemodynamic endpoints, developed progressive acidosis, and were volume-dependent to maintain

MAP and CPP (19, 20). Other animal model studies found that resuscitation from hemorrhagic shock with isotonic crystalloid solutions was associated with lower CPP, higher ICP, lower MAP, higher glutamate-mediated excitotoxic secondary brain injury and increased mitochondrial dysfunction, lower brain tissue oxygenation, more brain edema, larger brain lesion size, upregulation of inflammatory pathway genes, increased activation of coagulation, anticoagulation, and endothelial systems, greater degree of neurologic impairment, and markedly slower rate of neurologic recovery when compared to plasma products, regardless of the type of TBI model studied (17, 19–28).

Synthetic Colloids

Synthetic colloids, in particular hydroxyethyl starch (HES), are readily available, but their use in critically ill human patients is limited primarily due to increased rates of acute kidney injury and need for renal replacement therapy following administration (29). There are relatively few studies evaluating synthetic colloids in TBI patients, and all but one used experimental animal models. Formation of cerebral edema was greater in a rat model of mild to moderate TBI resuscitated with isovolemic hemodilution using 0.9 or 0.45% sodium chloride compared to whole blood or 6% HES 670/0.75, possibly from a reduction in colloid osmotic pressure (COP) (30). In pig models of TBI and hemorrhage testing various crystalloid and colloid infusion, resuscitation with 6% HES 670/0.75 in LRS required less total volume to achieve hemodynamic endpoints, resulted in a steady improvement in base excess and a CPP >70 mmHg by 270 min post-injury and resuscitation (19, 20). Animals were hypercoagulable in both the LRS and HES groups based on thromboelastographic testing, and there was no difference in transfusion requirement, time to wean from the ventilator, or mortality compared to animals resuscitated with 0.9% sodium chloride. In another pig model of TBI with polytrauma and hemorrhage, 0.9% sodium chloride, 6% HES 670/0.75, and fresh frozen plasma (FFP) were compared as resuscitation fluids (24). HES reduced edema and lesion size compared to 0.9% sodium chloride, but not as effectively as FFP.

The only identified clinical study specifically evaluating synthetic colloids in patients with TBI was a single-center retrospective cohort study of 171 people with severe TBI (31). In this cohort 78% of patients received 6% HES 200/0.5 during hospitalization. There was no association with mortality, change in serum creatinine, or establishment of renal injury. The Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) evaluated 6% HES 130/0.4 and pre-specified a TBI subgroup analysis (32). However, only a small number of patients with TBI were recruited preventing any reliable conclusion (32, 33).

Natural Colloids

The rationale for using natural colloids as a resuscitation fluid is to avoid or reduce the amount of isotonic crystalloid fluid infused thereby avoiding the complications such as increased brain edema (9, 34), and to avoid use of the synthetic colloids, which, in people, is associated with significant adverse outcomes in many critically ill populations (29). Albumin as a resuscitation fluid during TBI has been evaluated in animal models and human clinical trials with conflicting results. The most notable study was the SAFE (Saline vs. Albumin Fluid Evaluation) trial and subsequent *post-hoc* analysis (34, 35). The SAFE trial was a randomized controlled trial comparing 4% albumin to 0.9% sodium chloride for resuscitation from hemorrhagic shock. A secondary analysis of the subset of patients with hemorrhagic shock and TBI found the patients resuscitated with 4% albumin had higher mortality rate than the subset resuscitated with 0.9% saline (34, 36). This was in contrast to smaller single center and animal studies that suggested a beneficial effect of albumin (37, 38). The mechanism for this outcome cannot be determined from the SAFE trial because the study was not designed to answer this question (9, 34, 36).

Resuscitation with hypoosmolar solutions (including 4% albumin) has been associated with increased brain edema (36). These authors postulate that this may be the reason for increased mortality associated with 4% albumin resuscitation, and that the osmolality of an infusion solution rather than the COP may be more important in the pathogenesis of cerebral edema formation associated with resuscitation fluids (9, 36). Other authors suggest that with a loss of BBB integrity, any colloid might leak into the brain and pull water with it (39). The Lund Concept recommendations continue to support the use of 4% albumin (9) in spite of the evidence of harm (34, 36).

There is increasing evidence in the general trauma population that ratio-based resuscitation with high ratios of FFP to packed red blood cells confers a survival advantage to patients requiring massive transfusion (40). This may be due to avoidance of the complications associated with large-volume crystalloid resuscitation (41, 42). There is also evidence that FFP exerts a protective effect on the endothelium and endothelial glycocalyx layer (22, 41–43), and may protect or help to heal the BBB when administered early to patients with TBI (22, 42, 43). Plasma products have been evaluated as a resuscitation fluid in animal models and human patients with TBI. Fresh frozen plasma, lyophilized plasma, and spray-dried plasma perform similarly when compared to one another (23, 28, 43, 44), and consistently outperform resuscitation with crystalloid or colloid solutions (21–23, 26–28, 36, 42, 44–49).

In animal models of TBI, use of plasma products consistently resulted in favorable responses when compared to resuscitation with isotonic crystalloids (21–23, 25–28, 40–45, 47) or HES (26). Resuscitation from hemorrhagic shock with plasma products was associated with improved CPP, higher MAP, improved brain tissue oxygenation, and reduced brain edema and lesion size (21–23, 26). In addition, administration of plasma products resulted in diminished glutamate-mediated excitotoxic secondary brain injury and reduced mitochondrial dysfunction (21, 26), down-regulation of inflammatory pathway genes and expression of gene clusters mapping to increased metabolic and platelet signaling (26), a lesser degree of neurologic impairment, and markedly faster rate of neurologic recovery (28).

The results of human clinical data surrounding the use of plasma products to treat patients with TBI are mixed and complicated by small sample size and differences in protocols and study population. There are two single center, prospective, randomized trials evaluating the early empirical use of FFP in patients with severe closed head injury: one

with 63 patients receiving 5 ml/kg (50) and one with 90 patients receiving 10–15 ml/kg (51). Fresh frozen plasma or an equal volume of 0.9% sodium chloride was administered over 3–4 h following initial hemodynamic stabilization and CT scan. The fluid types and volumes used for initial stabilization are poorly described but may have included blood products, crystalloids, and/or colloids. In both studies, early empirical use of FFP was associated with an increase in delayed traumatic intracerebral hematoma formation. The study by Zhang (50) showed increased rate of blood transfusion and coagulopathy, but no mortality difference in patients receiving FFP, whereas the study by Etemadrezaie (51) showed increased mortality but no difference between groups for rate of coagulopathy (there was no comment on transfusion requirements).

Gruen (46) et al. reported the secondary analysis of a predefined subgroup of patients with TBI from the PAMPer trial. The PAMPer trial (52) was a multi-center, cluster-randomized, phase-3 superiority clinical trial comparing plasma administration to standard-care resuscitation in severely injured patients during air-medical transport, and the primary outcome was mortality at 30 days. The study enrolled patients transported from an outside referral emergency department and directly from the scene of the accident. Patients were randomized to receive plasma vs. no plasma in addition to standard care. From that cohort, a subset of patients with TBI were included in the secondary analysis. Among patients with TBI, the group receiving resuscitation with plasma during air transport had improved 30-day survival compared to those that did not. They also received less crystalloid fluid, vasopressors, and packed red blood cells in the first 24 h, had lower international normalized ratios, lower 24 h mortality, and lower 30-day mortality. The plasma group also had higher incidence of multiple organ failure, longer ICU stay, and longer hospital length of stay. Plasma treatment was associated with the greatest survival benefit in the sickest/most severely injured of these patients. Additionally, transport origin (scene of accident vs. hospital transfer) was used as a proxy for time-to-plasma resuscitation. When grouped by transport origin, patients transported from the scene of the accident who received plasma had lower 30-day mortality than those who did not receive plasma, while there was no difference between patients receiving plasma vs. no plasma when transported from a referral emergency department, suggesting that minimizing time from injury to administration may be important (46).

Retrospective studies also suggest patients with TBI benefit from early resuscitation with plasma (40, 53). Unlike the two single-center prospective trials already discussed, patients in these retrospective trials received plasma as part of the initial resuscitation. Jokar (53) et al. report on 1:1:1 (plasma:pRBC:platelet) ratio-based-resuscitation vs. non-ratio-based resuscitation in trauma patients with isolated TBI and intracranial hemorrhage. Patients receiving ratio-based resuscitation received more plasma and no crystalloid compared to non-ratio-based resuscitation, had significantly lower mortality compared to those who did not, and crystalloid administration was associated with increased odds of death. Additionally, there was no difference in progression of intracranial hemorrhage or rate of neurosurgical intervention between groups (53).

Chang (39) et al. evaluated early plasma transfusion during initial resuscitation in patients with isolated TBI without polytrauma and intracranial hemorrhage at a single center. Evaluation of the full cohort showed no difference in baseline characteristics or survival between patients receiving plasma and those who did not. Patients were then sub-grouped based on the dominant brain lesion: extradural hematoma, subdural hematoma, intraparenchymal contusion, subarachnoid hemorrhage, or multifocal intracranial hemorrhage. There were significant differences in age, mechanism of injury, hypoperfusion, injury severity, early plasma transfusion, and survival among the different subgroups. In the subgroup with multifocal intracranial hemorrhage early plasma transfusion was associated with improved survival. Compared to patients with extradural hematoma, subdural hematoma, intraparenchymal contusion, or subarachnoid hemorrhage, these patients were more likely to present with markers of more severe injury: severe TBI, hypotension, hypoperfusion, more severe injuries, and coagulopathy. Twenty-five percent of these patients received early plasma transfusion which was associated with improved in-hospital survival. Early plasma transfusion was not associated with improved survival in any of the other subgroups (39). It is difficult to make direct comparisons between any of these studies due to the significant differences in populations, protocols, and study design.

Hyperosmolar Fluids During Resuscitation

An intact BBB is required for a predictable response to osmolar gaps to occur (54–56). Following a significant TBI, cerebral edema may be reduced by a hyperosmolar fluid infusion (54, 57–59). Use of hyperosmolar solutions during initial resuscitation is not discussed in either of the human guidelines (8, 9) although they are evaluated in the experimental and human clinical literature. When used empirically in the prehospital setting as a low-volume resuscitation fluid, 7.5% HTS is well-tolerated but does not confer a survival benefit compared to isotonic crystalloid resuscitation (33, 60, 61). However, in patients with intracranial hypertension both HTS (3–23.4%) and mannitol effectively lower ICP (33, 62). In two experimental dog models of TBI and hemorrhage the animals were resuscitated with either 3% HTS (8 mL/kg) or LRS (16 mL/kg) (63, 64). Animals resuscitated with HTS had higher CPP, lower ICP, higher serum sodium and osmolarity, less cerebral edema, and faster return of pupil responses compared to animals resuscitated with LRS. When animals were further resuscitated by returning their shed blood to maintain MAP >70 mmHg there was no difference in total volume infused between groups (64). In a rat model of TBI and hemorrhage, HTS (7.5%) resuscitation was associated with improved long-term neuronal survival as well as faster and more complete

behavioral recovery compared to 0.9% sodium chloride or no resuscitation (65).

FLUID RESUSCITATION TECHNIQUE

The fluid administration and shock management technique might also matter, particularly in patients with uncontrolled hemorrhage. Current BTF (8) and damage control resuscitation guidelines (15) recommend strongly against hypotensive resuscitation in favor of resuscitation to a systolic BP 90–110 mmHg. There is evidence that even transient episodes of hypotension lead to irreversible secondary brain damage in a time- and dose-dependent manner (66–68). However, experimental data suggests normotensive resuscitation prior to hemorrhage control may not be the optimal strategy. Vrettos (18) et al. compared aggressive crystalloid resuscitation to no initial resuscitation in a pig model of TBI with hemorrhage. TBI was induced in anesthetized pigs followed by abdominal hemorrhage to a MAP of 30 mmHg. After 6 min of hypotension the animals were randomized and either resuscitated to a systolic BP of 80 mmHg with LRS or allowed to remain hypotensive. Animals surviving to 1 h post-injury then underwent surgical hemostasis and 1 h of resuscitation with shed blood. All animals in the early aggressive fluid resuscitation group died of exsanguination and hemorrhagic shock in less than an hour, none surviving to undergo surgical hemostasis and further resuscitation. Half of the animals in the hypotensive group survived to receive surgery and resuscitation. In the survivors, MAP, cardiac output, cerebral blood flow and oxygen measurements were restored to pre-hemorrhage levels. There was no evaluation of brain lesion size or any functional outcome in these animals. The authors suggest that while hypotension is suboptimal in TBI, bleeding to death leaves no chance of survival, and other resuscitation strategies need to be investigated.

In another pig TBI and uncontrolled abdominal hemorrhage model, resuscitating pigs with vasopressin plus 6% HES 670/0.75 in LRS increased blood pressure but failed to improve cerebral blood flow and increased abdominal hemorrhage volume compared to resuscitation with HES only and to no resuscitation (66). A third pig TBI and hemorrhage model compared FFP and 0.9% sodium chloride administered as either a large rapid bolus or slower stepwise resuscitation (27). Pigs underwent TBI and 40% blood loss, were kept hypotensive for 2 h, then resuscitated with FFP or 0.9% sodium chloride. The FFP group received the shed blood volume back as either a fast bolus (50 ml/min) or stepwise infusion starting at 2 mL/min and gradually increasing to 50 mL/min. The 0.9% sodium chloride group received 3x the shed blood volume either as a bolus at 165 mL/min or starting at 6 ml/min and gradually increasing to 165 mL/min. Animals were euthanized and tissue harvested after 6 h. Bolus FFP or 0.9% sodium chloride resulted in greater brain swelling but similar lesion size to stepwise FFP or 0.9% sodium chloride, suggesting that stepwise infusion is superior to rapid bolus. In addition, 0.9% sodium chloride infusion resulted in more swelling and a larger brain lesion when compared to both FFP infusion types.

MANAGING ELEVATED ICP WITH OSMOTHERAPY

Osmotherapy is the infusion of a hyperosmolar fluid with the intention of producing an osmolar gap and transferring brain parenchymal fluid into the vessels to be excreted in the urine. This reduces blood viscosity, which improves rheology resulting in constriction of pial arterioles (68–70). A direct effect at the site of injury may not be realized should blood flow to the site of injury be limited, or the BBB be disrupted. However, in regions where the BBB is intact, the osmolar gap may remove water that has accumulated in the brain cell and interstitium, and reduce ICP. The most common fluids used for osmotherapy include mannitol (20 and 25%) and HTS (3, 7.5, 24%). Their differences are summarized in **Table 1**. A key difference between the two fluids is that HTS can be used for dual purpose in treating hypovolemic shock as well as reduce cerebral edema. There is no strong evidence to support any recommendation for the use of osmotherapy for the treatment of traumatic intracranial hypertension or using one over another, and a summary of the evidence follows.

A single clinical veterinary study evaluating the effect of isosmotic mannitol and 3% HTS in two cats and one dog was identified (71). The animals were presented to a veterinary teaching hospital with naturally occurring head trauma, received immediate cardiovascular resuscitation with LRS, pain control with fentanyl, and antibiotic coverage with cefazolin when indicated. A brain MRI was performed within 12 h of presentation and as soon as the animals were considered stable. Animals suspected to have elevated ICP were instrumented for direct ICP monitoring immediately following imaging and randomized to receive either 18% mannitol or 3% HTS. ICP and CPP were recorded before and at five timepoints during the 120 min post-treatment. Patient one received 3% HTS and had no response to treatment. Patient two received 3% HTS resulting in an approximately 40% decrease in ICP and 15% increase in CPP. The ICP remained lower than baseline however the patient became hypotensive requiring further isotonic fluid resuscitation and dopamine to raise the MAP. This period of hypotension resulted in a decreased CPP, and the patient's response to 3% HTS was therefore classified as transient. The third patient received 18% mannitol. Initially the ICP decreased by 19% and the CPP returned to normal, however there was a rebound increase in ICP that was higher than pre-treatment values, and the CPP decreased again before gradually returning to normal over the 120-min monitoring period.

Numerous reviews and meta-analyses evaluate HTS and mannitol against various agents in the human clinical literature (33, 62, 72–82). In summary, the studies are heterogenous in population, dose, concentration and rate of fluid administered, therapeutic targets, and outcomes of interest. Therefore, the systematic reviews can only draw limited and general conclusions. The available evidence suggests that both mannitol

TABLE 1 | Characteristics of Mannitol and Hypertonic Saline.

	Mannitol	Hypertonic Saline
Base	6-carbon, alcohol sugar isomer of sorbitol	Sodium and chloride
Osmolarity (mOsm/L)	20%: 1100 25%: 1375	3%: 1027 (500 mmol/L) 7.5%: 2565 (1274 mmol/L) 23.4%: 8008 (4004 mmol/L)
Reflection coefficient	0.9	1.0
Molecular weight (Daltons)	182	
Diuretic effect	Excreted as is in urine and induces osmotic diuresis	Releases ANP
Additional effects	Oxygen-free radical scavenger	↑IV volume & ↑MAP Immunomodulator
Dose for treating intracranial hypertension	500–1000 mg/kg over 15 min. Can be repeated 2-3 X if effective	4-6 ml/kg of 7.5%
Dose for treating hypovolemia		4-7 ml/kg of 7.5% or 4-7 ml/kg 1 part 23.4% mixed with 3 parts HES

and HTS effectively lower ICP, but there is not enough evidence to suggest one fluid is superior, although a few studies suggest HTS may have slightly fewer treatment failures in patients with refractory intracranial hypertension compared to mannitol (62, 73–76, 78, 83, 84). Additionally, HTS avoids diuresis and increases cardiac preload, favorably impacting cerebral perfusion (33, 79). Mannitol is associated with a well-documented rebound phenomenon in patients with intracranial hemorrhage and brain tumors, occurring in about 12% of patients (85–89). A rebound phenomenon was defined in a Cochrane review by Chen (76) et al. as 'intracranial pressure rising above its original level after hyperosmolar therapy.' However, the rebound phenomenon occurring in patients with TBI is only mentioned in passing in a single study included in the Cochrane review (76) and in the veterinary pilot study (71). Despite effective reduction of ICP, neither HTS nor mannitol has clinical evidence supporting improved survival or long-term neurologic outcome (33, 75, 81).

The optimal dose has not been determined for either mannitol or HTS. There is some evidence that higher doses of mannitol (∼ 1.0–1.5g/kg) might be associated with greater reduction of ICP and less rebound phenomenon compared to lower doses of mannitol, although the data surrounding the dose-relationship with rebound phenomenon is conflicting (80, 90–93). A specific, evidence-based dosing strategy for HTS cannot be determined at this time due to insufficient evidence and profound heterogeneity among the various studies. In the veterinary clinical study (71) noted previously, the 2 cats received 5.3 ml/kg of 3% HTS IV over 5 min. One had no response to therapy and the other had an approximately 40% decrease in ICP. The Neurocritical Care Society has published guidelines for acute treatment of cerebral edema in human neurocritical care patients with TBI and recommends symptom-based bolus dosing over sodium-target-based dosing (94).

Continuous infusion of HTS in patients with various pathologies has been evaluated in a small single center trial and was compared in a pooled analysis against intermittent bolus therapy from two other trials (95). The hazards ratio for survival showed a 90-day functional outcome with continuous infusion to be significantly greater compared to bolus therapy. There were no significant adverse effects observed with HTS continuous infusion (96, 97). This is in contrast to pediatric patients, where sustained hypernatremia is associated with thrombocytopenia, kidney failure, neutropenia, and ARDS (97–101). The recently published COBI (Continuous hyperosmolar therapy (20% HTS) in Brain-Injured patients) trial compared functional outcome at 6 months between standard care alone and continuous therapy with 20% HTS in 370 adults (102). All patients received recommended interventions based on the most recent BTF guidelines. The treatment group received a 1 h bolus infusion adjusted to their measured serum sodium level within 24 h of trauma, which was immediately followed by a 0.5–1 g/kg/h continuous infusion of saline. Serum sodium levels were monitored, and the infusion concentration adjusted to prevent an elevation in serum sodium >155 mmol/L for a minimum treatment period of 48 h and only while intracranial hypertension remained a risk. The infusion was stopped once 12 h had passed following the suspension of all specific therapies for intracranial hypertension. Although the study was underpowered to detect a clinically important difference, the authors concluded that in patients with moderate to severe TBI, there was no significant difference in neurological status between the treatment and control group.

ADDITIONAL CONSIDERATIONS WITH HTS AND MANNITOL

Several local and systemic pathophysiological consequences contribute to secondary injury of the brain which may be mitigated by HTS and/or mannitol. Hypovolemia, hypotension, cerebral vasospasm, and altered blood flow result in activation of systemic inflammation and hypoxemia. In the brain, cerebral leukocytes congregate in injured areas and initiate vasodilation and peroxidase/protease-mediated

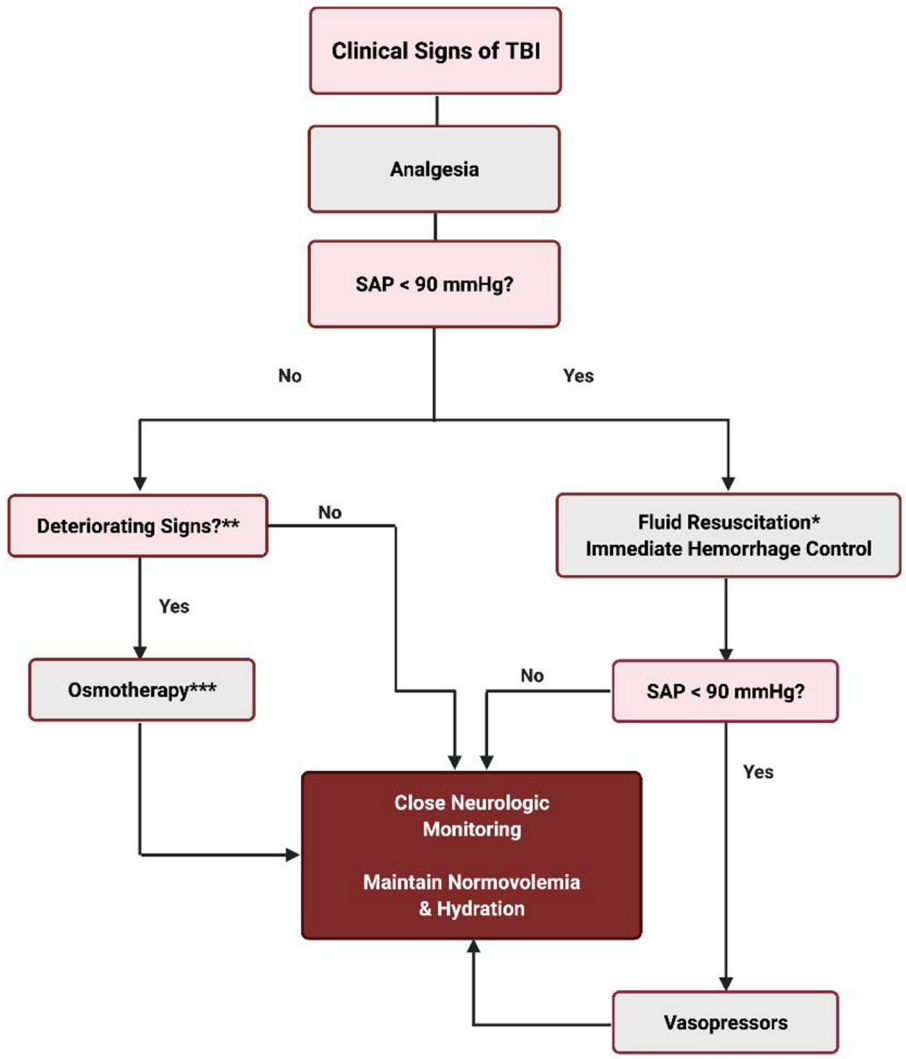

FIGURE 1 | Fluid therapy for the TBI patient. *Fluid resuscitation techniques can be any one of the following or a combination thereof: (1) 10–20 ml/kg crystalloids (Plasma Lyte or Normosol-R) IV rapid infusion up to 60–90 ml/kg. (2) 5–10 ml/kg 6% HES (tetrastarch) IV rapid infusion up to 40–50 ml/kg. (3) 5–10 ml/kg plasma rapid infusion IV up to 20–30 ml/kg. (4) 3–4 ml/kg 7% HTS IV over 10–15 min. (5) whole blood or pRBC, if indicated. **Altered level of consciousness with or without bilateral or unilateral miotic pupils; unresponsive mid range pupil(s) or mydriasis; loss of the oculocephalic reflex; bradycardia with hypertension (Cushing reflex); posturing (opisthotonus, decerebellate, decerebrate); alteration of the respiratory pattern. ***1 g/kg mannitol IV up to 3 doses q60–90 min OR 3–4 ml/kg 7% HTS IV.

cell death (101, 103). Dysfunction of cell-mediated immunity can occur and may be moderated by HTS (104–107).

Hypoxemia results in the depletion of ATP, cellular membrane ion pump malfunction, intracellular sodium accumulation and endothelial cell swelling. This can narrow the vascular lumen causing red blood cells to pass through vessels with more difficulty, and rupture or cause premature apoptosis of neuronal cells. In addition, brain injury can induce extensive neuronal depolarization which decreases extracellular sodium reversing the direction of the Na-glutamate cotransporter, causing an increase in extracellular glutamate, compounding neurotoxicity (107–110). Using HTS during resuscitation improves alveolar gas exchange by reducing extravascular lung volume, reverses endothelial and red blood cell swelling improving blood flow and oxygen delivery and restores extracellular sodium and cellular action potential, moderating glutamate toxicity in the brain (111–116).

During reperfusion of hypoxemic tissue, the production of radical oxygen species can propagate tissue injury. Mannitol may limit the secondary oxidative injury in the brain by scavenging radical oxygen species (117).

Hypotension caused by a decrease in systemic vascular resistance and/or a vagal-mediated reflex after the rapid administration of HTS has been reported to occur in humans, dogs, and rabbits (118–120). This appears to be transient as it is followed by an increase in MAP and myocardial contractility.

SUGGESTED THERAPEUTIC APPROACH

It is clear from the information available that therapeutic recommendations for fluid therapy in the dog or cat with TBI continue to remain the clinician's choice. Maximizing CPP by correcting systemic hypotension is a cornerstone to management of TBI, although this has to be done carefully when also treating severe hemorrhage resulting from polytrauma. Hypovolemia is treated with isotonic crystalloids, hypertonic saline, and/or colloids. A decline in neurological status in the non-hypotensive patient warrants osmotherapy. The authors approach to fluid resuscitation of the small animal patient with TBI is outlined in **Figure 1**.

ON THE HORIZON

Various fluid additives and novel molecules are being investigated to identify the optimal resuscitation fluid for patients with TBI. One combination that stands out is HTS containing adenosine, lidocaine, and magnesium. This combination appears to play a protective role in a variety of life-threatening conditions in animal models of sepsis (121–124), non-compressible hemorrhagic shock (125–127), and TBI from non-compressible hemorrhage (128). Interestingly, the drugs do not confer benefit when used individually, and magnesium sulfate alone might increase mortality in humans with TBI (129). LRS with added drag-reducing molecules has been evaluated in a rat model, and appears to improve cerebral microcirculation, increase brain tissue oxygenation, and reduce neuron loss, despite lower mean arterial pressure (130).

Modified hemoglobin-based oxygen carriers (HBOCs) that have reduced nitric oxide scavenging and oxygen-free radical generation are being evaluated as resuscitation fluids in animal models of TBI and hemorrhagic shock (131–133). Polynitroxylated-pegylated hemoglobin (PNPH) is a novel HBOC bovine-origin carboxyhemoglobin with covalently labeled nitroxide moieties being evaluated for use as a small-volume resuscitation fluid (132–134). The polynitroxylation of the hemoglobin molecule has antioxidant properties and prevents nitric oxide scavenging, while the polyethylene glycol side chains create a "hydrating shell" that has a strong oncotic effect useful in resuscitation (131). PNPH has also been evaluated in mouse models of TBI with hemorrhage (131–133), and compared with crystalloid and whole blood resuscitation (131). Mice resuscitated with PNPH required smaller volume fluid resuscitation and had higher mean arterial blood pressure that remained normal and stable through to the end of the experiment without the need for additional fluid infusion. In addition, they had a lower ICP and markedly less brain edema compared to those resuscitated with crystalloid or whole blood.

Dodecafluoropentane emulsion is an oxygen-carrying perfluorocarbon emulsion also under investigation for use in patients with TBI. In humans it has a short half-life (90 min) and is cleared via exhalation from the lungs (135). It is administered IV, travels to the lungs where it picks up oxygen, then to the tissues where it delivers oxygen. It has been evaluated in a rat model of TBI where brain tissue oxygen levels increased to 146% of the post-injury, pre-treatment level, with no effect on systemic blood pressure, heart rate, biochemical parameters, or blood gas measurements (135, 136). Further evaluation is needed before these therapies can be recommended in clinical practice.

CONCLUSION

There is a paucity of information covering treatment of TBI in dogs and cats, which is limited to experimental data in primarily pigs and rats, and clinical data collected from human studies. Response to treatment can be complicated by acute hemorrhage. The research and limited clinical studies examined do not provide sufficient evidence for a preferred fluid type, although it appears that infusion of LRS is less desirable than other isotonic crystalloids, and the use of plasma products during resuscitation may convey an improved outcome. To further the knowledge base on therapeutic interventions for TBI in dogs and cats, future clinical studies should focus on the effect of specific fluid prescriptions and osmotic agents on short- and long-term outcome.

AUTHOR CONTRIBUTIONS

Both authors contributed to the body of the paper, reference research, and editing.

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REVIEW
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Effects of IV Fluids in Dogs and Cats With Kidney Failure

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Intravenous fluid therapy has long been the mainstay of treatment of kidney disease, including acute kidney injury and uremic crisis associated with chronic kidney disease. Careful management of fluid dose is critical, as animals with kidney disease may have marked derangements in their ability to regulate fluid homeostasis and acid-base status. Understanding of the physiology of renal fluid handling is necessary, along with repeated attention to parameters of fluid status, electrolytes, and acid-base balance, to achieve optimal hydration status and avoid further damage or decrease in function from dehydration or overhydration.

Keywords: renal, kidney, acute kidney injury, chronic kidney disease, oliguria, anuria, polyuria

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INTRODUCTION

Fluid therapy is the most commonly administered intravenous treatment for hospitalized veterinary patients. Adequate fluid resuscitation is essential for the restoration of cardiac output, systemic blood pressure, and renal perfusion. Achieving an appropriate level of volume management requires knowledge of underlying pathophysiology, evaluation of volume status, selection of appropriate solution for volume repletion and maintenance, and modulation of the tissue perfusion (1).

Recently, Hoste et al. (2) proposed four distinct phases (ROSE) of intravenous fluid therapy for humans with critical illness: (R) resuscitation, (O) optimization, (S) stabilization, (E) evacuation. In overview, the *resuscitation phase* anticipates an escalation of fluid therapy in patients with life-threatening shock (low blood pressure, signs of impaired perfusion, or both) and is characterized by the use of *fluid bolus* therapy (rapid infusion to correct hypotensive shock; ∼10 ml/kg balanced isotonic crystalloid over 15 min; typically not exceeding a total of three boluses). When transitioning to the *optimization phase*, the patient should no longer be in immediate life-threatening danger, but in a stage of compensatory shock and high risk for decompensation. At this point, additional fluid therapy is given more cautiously with the intent of optimizing cardiac function and improving tissue perfusion. The goal is to administer the volume necessary to alleviate organ dysfunction. *Fluid challenges*, defined as a small volume over short period of time (∼5 ml/kg over 20 min), are typically given in this phase to test the effects of delivering more volume (3). Some patients may bypass the *resuscitation phase* (with no evidence of hypotension) and present to the hospital in a compensated state. In these first two phases, compensatory neuroendocrine reflexes and possible renal dysfunction result in sodium and water retention, contributing to a positive fluid balance. Progression to the *stabilization phase* encompasses a point at which the patient is at steady state without signs of shock. Fluid therapy in this phase is used for ongoing maintenance losses (renal, gastrointestinal, insensible); as well as rehydration if the patient is experiencing ongoing losses due to unresolved pathology. Patients may experience temporary deterioration and revert back to the *optimization phase* if faced with a newly developed infection or organ dysfunction. Lastly, the *evacuation phase* is characterized by the removal of fluids and promotes a negative fluid

balance (2, 4). This may need to be achieved with low doses of loop-diuretics (authors suggest 0.25–0.5 mg/kg IV). The physiological response to fluids and underlying conditions are dynamic over time, thus fluid administration should be based on repeated assessment of cumulative fluid balance and hemodynamic status. Generally, hemodynamic status can be assessed using dynamic testing to evaluate fluid responsiveness (5).

Interest in intravenous fluid therapy and its side effects has increased in recent years. Many trials have investigated the colloid/crystalloid debate, while others have provided guidance on selecting the optimal crystalloid solution (6). In addition, the role of chloride and its detrimental effect on kidney function has garnered much attention (7–10). Much of the research has focused on fluid therapy in the resuscitation phase, in which people receive large amounts of fluid over a short period of time. In reality, hospitalized people receive fluids and electrolytes for other reasons including maintenance therapy, medications, and replacement for existing or ongoing losses. The cumulative fluid delivery frequently exceeds fluid loss, leading to a net positive fluid balance or "fluid creep." With this principle in place, additional considerations need to be made for renal patients with altered sodium handling.

PATHOPHYSIOLOGY

The primary function of the kidney is to maintain a stable extracellular compartment by selective retention/elimination of water, electrolytes, and other solutes. This is achieved via filtration of the circulating blood into ultrafiltrate from the plasma, selective reabsorption from tubular fluid into peritubular capillary blood, and selective secretion from peritubular capillary blood into the tubular fluid. Glomerular filtration (*net ultrafiltration pressure*) is determined by the difference in hydrostatic and oncotic pressure gradients between the glomerular plasma and the filtrate in Bowman space. Each nephron has its own single-nephron glomerular filtration rate (SNGFR), and the sum of the SNGFRs of the functioning nephrons make up the total glomerular filtration rate (GFR). Maintaining a normal GFR is dependent on adequate renal perfusion.

Acute kidney injury (AKI) is defined as a rapid decline in GFR through the measurement of serum creatinine and urine output. There are inherent challenges with this definition as creatinine is poorly correlated with GFR at low levels of renal dysfunction (11). Clinically, AKI is grouped into three etiologies: pre-renal, renal, and post-renal. Pre-renal azotemia is characterized by a decrease in GFR due to a decrease in renal perfusion pressure without damage to the renal parenchyma (12). Post-renal causes of AKI are characterized by acute obstruction of urinary flow, leading to increases in intratubular pressure, impaired renal blood flow and inflammatory processes, and decreased GFR (13). Renal azotemia is associated with a sudden onset of renal parenchymal injury, characterized by the kidneys inability to meet excretory, metabolic, and endocrine demands of the body. AKI represents a continuum of renal injury from mild, clinically inapparent nephron loss to severe acute renal failure requiring renal replacement therapy. The International Renal Interest Society (IRIS) AKI Grading scheme has been developed in veterinary medicine to determine appropriate grading in animals with AKI (14).

Intrinsic renal etiologies can be challenging to evaluate due to a wide variety of injuries that can occur to the kidney. In general, renal damage can be divided into four major structural groupings: the tubules, glomeruli, interstitium, and intra-renal blood vessels. Tubular damage can arise from either ischemic injury (decreased renal perfusion) or nephrotoxic compounds (exogenous and endogenous). Severe acute glomerulonephritis secondary to immune-complex disease causes glomerular damage. Interstitial damage can result from acute interstitial nephritis secondary to medications or infectious etiologies (leptospirosis, pyelonephritis, etc.). Lastly, vascular damage can occur secondary to injury to intra-renal vessels (thrombosis, hypertension, etc.), subsequently decreasing renal perfusion and diminishing GFR (15). Ischemia and nephrotoxic agents (e.g., certain drugs, plants, ethylene glycol, etc.) account for the majority of renal injury in human medicine as well as veterinary medicine (16).

Renal tubular injury is associated with a decrease in GFR and is divided into different phases of AKI, which are directly related to the cellular events that occur during the injury and recovery process. The *initiation phase* occurs when renal blood flow decreases, resulting in cellular ATP depletion and subsequent tubular epithelial cell injury. These changes alter the ability of tubular epithelial cells and vascular endothelial cells to maintain normal renal function (reabsorption and secretion), as well as up-regulate a variety of chemokines and cytokines to initiate an inflammatory cascade (17). The *extension phase* is characterized by continued hypoxia following the initial ischemic event and an inflammatory response, most prominent in the outer medullary region of the kidney. During this phase, vascular endothelial damage likely plays a key role in the continued ischemia of the tubular epithelium, as well as the inflammatory response. Cells in the outer medullary region undergo injury and death via necrosis and apoptosis (18). The cellular injury in this region leads to the continual reduction in GFR, whereas cells of the proximal tubule in the outer cortex, where blood flow has returned, undergo cellular repair and improve morphologically (19). The *maintenance phase* consists of cells undergoing repair, migration, apoptosis, and proliferation to reestablish and maintain cellular and tubular integrity. The GFR usually remains stable at the level determined by the severity of the initial event. Cellular repair and reorganization results in slowly improving cellular function, setting the stage for improvement in organ function. Blood flow returns toward normal and epithelial cells establish intracellular and intercellular homeostasis (19). During the *recovery phase*, cellular differentiation continues, epithelial polarity is re-established, and normal cellular and organ function returns (20). Alternatively, renal repair can be maladaptive with inflammation, fibrosis, and vascular rarefaction leading to persistent cell and tissue malfunction and eventually chronic kidney disease (21). AKI and chronic kidney disease (CKD)

are increasingly recognized as related entities representing a continuum of disease (22).

The assessment of renal recovery is controversial with a lack of clear, defined parameters. Despite the limitations, the most obvious definition of full recovery from AKI is the absence of AKI criteria. Partial recovery is defined as a fall in AKI grade. Recovery may occur early, after the insult (within 7 days), or later, during the proposed period of acute kidney disease (AKD), which is defined as AKI persisting for 7–90 days (23). Lack of complete recovery in the first 90 days is defined as CKD.

Disruption of normal renal function impairs maintenance of homeostasis. A normochloremic high anion gap metabolic acidosis is common, due to inadequate excretion of organic and inorganic acids such as phosphate and sulfate. Hyperkalemia is also common when urine production is low and distal tubular secretion of potassium is impaired. Conversely, hypokalemia may develop with polyuria, as the high urine flow through the distal tubule enhances potassium secretion by maintaining a concentration gradient between the tubular cells and the ultrafiltrate in the tubule lumen. Disorders of sodium are variable and depend on the degree of impairment of sodium reabsorption relative to water excretion. Because of impaired filtration and thus excretion of phosphate, leading to hyperphosphatemia, an ionized hypocalemia may develop acutely.

AIMS OF FLUID RESUSCITATION

The physiological rationale for fluid administration in AKI and CKD is to optimize intravascular circulating volume, increase cardiac output and perfusion pressure, with the aim of improving renal blood flow, renal oxygen supply, and GFR (**Table 1**). Hypotension is a strong risk factor for AKI, yet preserving systemic arterial pressure alone is not adequate for renal perfusion. Renal tissue perfusion relies on the pressure in the post-glomerular arterioles, which is often much lower than the systemic MAP (21). Conversely, fluid resuscitation beyond correction of hypovolemia does not increase the chances of renal recovery. Excessive fluid administration has been associated with the development of AKI, secondary to intrarenal compartment syndrome and venous congestion, attributed to the kidneys being encapsulated organs (24, 25). It is imperative to understand the physiological response to fluids and underlying condition related to AKI are dynamic, thus fluid administration should be based on repeated assessments of the patient and relevant biomarkers. Overall fluid and hemodynamic status, using dynamic tests of fluid responsiveness are utilized to determine the need for additional fluid therapy (5). The clinician is forced to walk a tight rope between too few fluids, which can lead to further progression of AKI from ongoing renal ischemia, and too much fluids leading to systemic complications and organ dysfunction.

FLUID TYPES

Fluids are differentiated into crystalloids and colloids. Disregarding the impact of fluid overload, there is growing evidence that renal function is affected by the type of fluid and certain fluids are associated with an increased risk of AKI (24, 26, 27).

TABLE 1 | Goals of fluid resuscitation in AKI.

- Optimize intravascular circulating volume
- Increase cardiac output
- Improve perfusion pressure
- Improve renal blood flow, renal oxygen supply, and GFR
- Dislodge debris and casts obstructing tubules

ISOTONIC CRYSTALLOIDS

Isotonic crystalloids are the accepted first-line IV fluid in most ICU patients. There is ongoing research as to which isotonic crystalloid, 0.9% NaCl vs. a buffered crystalloid (LRS, Plasma-Lyte, Hartmann's), is appropriate in people at risk for AKI. The impact of chloride concentration on renal function has been researched in a Greyhound model, showing that increasing plasma chloride levels produce progressive renal vasoconstriction and decreased GFR. These effects appeared to be related to tubular chloride reabsorption (28). Both animal research and studies in healthy human volunteers suggest that hyperchloremia may lead to renal vasoconstriction, reduction in renal cortical tissue perfusion and glomerular filtration, along with longer periods of fluid retention compared with buffered crystalloids (29).

Clinical trials comparing various crystalloid fluids in critically ill people at risk of AKI have produced conflicting results (7, 9, 10, 30). The SMART and SALT-ED trials are the largest randomized controlled trials comparing 0.9% NaCl and buffered crystalloids. Both found a significant reduction in the risk of major kidney events within 30 days, in the group treated with buffered solutions (9, 10). Despite these findings, the optimal fluid in people at risk of AKI has not been identified. It is of the authors opinion that balanced crystalloids should be used for resuscitation and replacement therapy. Dextrose-containing solutions should not be used as a replacement solution unless the patient is hypoglycemic or a neonate/infant.

HYPOTONIC CRYSTALLOIDS

Maintenance solutions (hypotonic crystalloids) are administered to meet the patient's basal requirements of water and electrolytes. Specific maintenance solutions are commercially available but are far from ideal. Studies in people have shown over the course of an ICU admission, a substantial amount of daily fluid volume is delivered with maintenance/replacement fluids, medications, and nutrition compared to resuscitation fluids (31). Generally, the overall sodium and chloride load administered with maintenance and replacement fluids is not taken into consideration, even though these fluids account for a large portion of the daily fluid volume in these patients. There is debate whether isotonic or hypotonic solutions should be used for maintenance fluid therapy. Much of the data in children has showed a possible risk of hyponatremia (32, 33). Studies in human adults indicate

a more positive fluid balance and decreased urine output with isotonic solutions compared to hypotonic solutions (34, 35). These studies bring to light the concept of "fluid creep" secondary to high daily sodium administration with isotonic crystalloids leading to fluid retention. Further studies in patients with AKI are needed to make a recommendation, but in theory these patients with altered sodium handling and higher chloride concentrations reaching the macula densa would benefit from a hypotonic solution in the *stabilization phase*. At this stage, the authors preferentially use hypotonic solutions to reduce sodium load in animals with renal dysfunction. Monitoring the animal's electrolytes and acid-base status frequently is essential for prescribing the appropriate fluid during the resuscitation and early stabilization phase.

SYNTHETIC COLLOIDS

In human medicine, the administration of synthetic colloids has been linked with the development of acute kidney injury (AKI) and the need for renal replacement therapy (RRT) in ICU patients, especially those with sepsis (27, 36). Findings from meta-analyses suggest this may depend on patient cohort, but did confirm a higher risk of AKI and conflicting reports on mortality (37). In veterinary medicine, there is inconclusive evidence on the development of AKI in dogs and cats treated with hydroxyethyl starches (HES). The majority of the studies are retrospective, with inconsistent definitions of AKI (38–41). Extrapolating from human medicine, in most clinical situations, the risks outweigh the benefits and alternative volume replacement therapies should be used in place of HES.

NATURAL COLLOIDS

Albumin is a natural colloid, specifically studied in resuscitation, that has not been shown to have consistent survival benefit. Although, albumin is considered safe in people at risk or with established AKI, studies are needed to assess potential benefits (24, 26, 42). The most recent Surviving Sepsis Campaign recommendations state that albumin in addition to crystalloids may be considered in limited quantities for early resuscitation and subsequent intravascular volume replacement in people with sepsis or septic shock (43). HES should be avoided in this patient population, thus other colloids (FFP and albumin) may be considered in limited quantities. There are no studies in veterinary medicine regarding the use of FFP or albumin in dogs or cats with renal dysfunction.

FLUID DOSE

There are few evidence-based studies evaluating the dose response of intravenous fluids in animals with kidney dysfunction. Standard formulas for what is commonly called a maintenance intravenous fluid rate make two presumptions, namely that animals have similar evaporative losses and that urine output is "average" (1–2 mL/kg/h). In patients with renal dysfunction, standard maintenance formulas do not apply and fluid requirements must be assessed on an individual basis. Evaporative losses in dogs and cats are predominantly through the respiratory tract, as perspiration is generally negligible, and salivary and fecal losses are generally not accounted for when determining fluid balance. Respiratory losses can be quite dissimilar and are impacted by environmental temperature and humidity, and by patient activity level. In one study of healthy dogs, evaporative losses varied from 8.1 to 75.7 ml/kg/day, with a mean of 27 mL/kg/day (44–46). Barking and panting increased evaporative loss compared to losses in quiet dogs. In cats, insensible loss ranged from 12.4 to 29 ml/kg/day in different studies (44, 47, 48). Insensible loss is generally considered to be 22 ml/kg/day, regardless of demeanor. In the animal with kidney disease, urine volume is highly variable, ranging from extreme polyuria to anuria, necessitating adjustment of fluid administration rates based on the specific, and changing individual animal fluid requirements. Accurate urine output quantification is obtained through the placement of a urinary catheter. Alternatively, if urine cannot be accurately measured due to the inability to place a urinary catheter, a towel or diaper with a pre-specified weight can be placed in the cage. The difference in the weight of the towel or diaper when the animal urinates is approximately equal to the urine produced (1 g increase in weight = 1 mL urine).

Westgren et al. evaluated 11 dogs with suspected kidney disease using scintigraphy to measure GFR before and after a 15 ml/kg intravenous bolus of crystalloid fluid (49). The GFR appeared to increase 31% after the fluid bolus when measurements were calculated based on weight. However, when GFR was evaluated based on plasma volume, there was no change in GFR after fluid therapy. Given the effects that a fluid bolus can have on renal dynamics, this new method of calculating GFR suggests that fluid therapy does not acutely increase GFR, although the technique needs further validation.

In one study of systemically healthy dogs undergoing an orthopedic surgery and receiving standard intraoperative fluid rates (10 ml/kg/h of lactated Ringers solution), the median urine output was 0.46 mL/kg/h (50). GFR was stable during anesthesia. These dogs gained a median of 1.1 L of fluid (3.4% of pre-anesthesia body weight) over the 4-h anesthetic period, which was mostly distributed to the extracellular space, despite having normal kidney function. The neurohumoral effects of anesthesia appear to be able to affect renal hemodynamics even in normal animals and the effects of depth of anesthesia on urine output requires further investigation.

Brandstrup et al. compared goal directed therapy to a zero-balance approach in humans undergoing colorectal surgery (51). In the goal directed approach, fluid was administered to maintain near maximal stroke volume, whereas the zero-balance approach only replaced fluid losses. There was no difference in outcomes. Thus, a zero-balance approach appears safe and requires less invasive monitoring. Similar studies in clinical veterinary patients with kidney disease do not exist, although this approach merits investigation. Zero-balance fluid administration can be achieved by monitoring urine output and adjusting fluid dose accordingly (**Table 2**).

TABLE 2 | Fluid dose guidelines.

- Resuscitation Phase: 10 ml/kg over 15 min, up to 3 boluses
- Optimization Phase: 5 ml/kg over 20 min
- Stabilization Phase*: Replace insensible loss at 22 ml/kg/day plus replacement of urine volume and additional loss (such as vomiting). The volume of medications and nutrition account for part of the fluid administered; the remaining volume is typically administered as a crystalloid fluid.
- Evacuation Phase: Decrease fluid dose by 10–20% every 12–24 h and monitor for dehydration

Presumes any dehydration deficit was corrected during resuscitation and optimization phases. If volume overload already exists from prior fluid therapy, decrease fluid rate to allow correction of the overload over ∼24 h.

COMPLICATIONS

Fluid overload is a commonly mentioned negative side effect of intravenous fluid therapy, especially in patients with initial renal dysfunction. It is well-documented in humans, and sparse evidence in veterinary medicine indicates that fluid overload contributes to progression of kidney dysfunction and increase in mortality (52–58). In addition, fluid overload has severe consequences affecting many different organs including the central nervous system, cardiovascular, pulmonary, hepatic, renal, and gastrointestinal tract (**Figure 1**) (4, 59). Excessive fluid administration is an iatrogenic complication that results in renal congestion, subsequently worsening renal perfusion and GFR due to interstitial edema. This is an area of harm seen in human and veterinary patients in attempts to "diuresis" the kidneys, ultimately leading to progressive renal dysfunction. Monitoring urine output in conscious animals is a sensitive and early marker for the detection of AKI, but also enhances the clinician's ability to track fluid overload and assess response to therapy. Cumulative fluid balance is the sum total of fluid accumulation over a set period of time and the percentage of fluid accumulation is defined by dividing the cumulative fluid balance by the patient's baseline body weight and multiplying by 100%. Diuretics remain a valid therapy for relieving symptoms and improving pathophysiological states of fluid overload, even in people with renal dysfunction (60–62). A urine output of 3–4 ml/kg/h after diuretic use has been shown to rarely cause intravascular volume depletion as intravascular refilling can equilibrate at that rate (25). With the limitations in detecting early signs of AKI due to the lack of active renal biomarkers in veterinary medicine, the authors recommend placing a urinary catheter in unstable cardiovascular, azotemic people to accurately monitor urine production. Because serum creatinine and oliguria are often late signs of significant AKI, a functional assessment of renal tubular function can indicate risk of AKI progression. Furosemide is a loop diuretic with ideal pharmacokinetic properties to assess tubular function. It is not effectively filtered by the glomerulus but is bound to serum proteins and gains access to the tubular lumen via active secretion in the proximal tubule. Once in the tubular lumen, furosemide inhibits active chloride transport throughout the ascending thick limb of Henle, preventing sodium reabsorption and inducing naturesis to increase urine flow (63). A furosemide stress test (1–1.5 mg/kg IV bolus) can be administered to oliguric patients that are assessed to be euvolemic or fluid overloaded to accurately determine AKI progression and need for renal replacement therapy (64). In human medicine, a 2-h urine cutoff of <200 mL produced the best sensitivity (87.1%) and specificity (84.1%) and was a predictor in progression of AKI (63). Unfortunately, this has not been studied in veterinary medicine, but extrapolating from humans, a response of 1.5 ml/kg/h roughly equates to the 200 mL over the 2 h time interval. Repeated administration of furosemide in a non-responsive patient can lead to adverse effects such as ototoxicity, which has been reported in humans.

The use of diuretics to increase urine output does not improve renal function. If renal replacement therapy is not available, diuretics may help control hyperkalemia by increasing distal tubular flow and allow more liberal administration of nutrition and medications with less risk of volume overload. Despite the widespread use of diuretics in human medicine, there are few guidelines pertaining to the dose and interval of administering furosemide. A recent meta-analysis in humans showed continuous furosemide was associated with greater diuretic effect in total urine output as compared to bolus dosing, although neither had any difference in mortality (65). The authors recommend the following doses (1–2 mg/kg IV q 6–8 h or 0.25–0.5 mg/kg/h IV) when administering furosemide. Hyperkalemia can be treated temporarily by causing an intracellular shift using regular insulin (0.5 u/kg IV with 1 g/kg IV dextrose). Beta-adrenergic agonists (e.g., terbutaline, albuterol) can be used as adjunctive therapy to shift potassium intracellularly but may require higher doses than need for bronchodilation. Bicarbonate therapy should be considered in dogs and cats with AKI and severe metabolic acidosis (i.e., pH < 7.1 or serum bicarbonate <12 mEq/L). A significant beneficial effect has been shown in humans with AKI and severe metabolic acidosis to decrease the need for renal replacement therapy and overall mortality (66, 67).

CLINICAL CONTEXT

Management of dogs and cats with AKI involves treating the underlying cause and providing time for the kidneys to repair themselves. Appropriate fluid therapy is paramount in the medical management of AKI, aiming to restore hydration and euvolemia. The preconceived notion to increase the fluid rate and force diuresis in animals with AKI must be absolutely avoided. This is especially true in animals with established oliguria or a relative oliguria, in which they are unable to appropriately respond by increasing urine production, thus developing generalized edema that directly exacerbates further organ dysfunction. If the animal is not able to remove the excess fluid due to lack of kidney function, renal replacement therapy is indicated to help facilitate fluid removal and achieve appropriate fluid balance. It is only once the animal has established a consistent urine output and advanced to the polyuric phase, that it becomes reasonable to increase the fluid rate to match urine output. Emphasis is placed on the importance of frequent patient

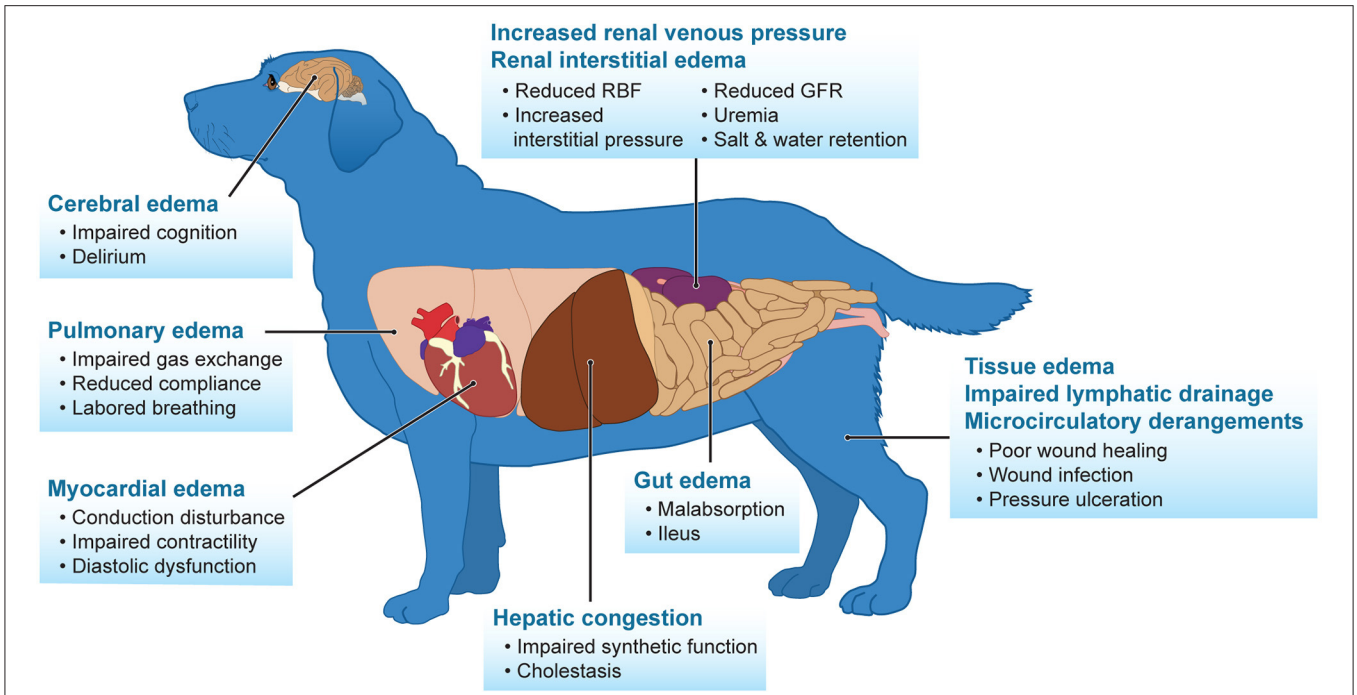

FIGURE 1 | Fluid overload adversely impacts many body systems. Adapted from Prowle et al. (25).

assessments (cumulative fluid balance) to determine the fluid needs of these patients.

Fluids should be gradually tapered when hydration and urine production are restored, fluid "in" and urine "out" are matched, and the serum creatinine has plateaued (i.e., no further improvement at this stage). The authors recommend decreasing the fluid rate by 15–20% every 8 h, with the goal of discontinuing intravenous fluids in a 48 h period. It is not uncommon for animals with AKI to require a feeding tube (esophagostomy or gastrostomy) to not only administer proper nutrition and meet the demands of the hypercatabolic state, but also supplement enteral fluids in a markedly polyuric animal. The feeding tube allows the owner to play an integral role in the recovery phase of AKI as well as reduce the time and cost associated with hospitalization. A less physiologic option for maintaining hydration in an animal with AKI is the use of subcutaneous fluids. Subcutaneous fluids involve administration of large quantities of "salt water" (LRS, 0.9% NaCl), making this option less than ideal for animals with intrinsic renal dysfunction.

Consideration for fluid type (hypotonic and balanced isotonic) along with reduction in cumulative sodium load is more physiologic for dysfunctional kidneys. Additional studies are needed to characterize the urine chemistry of dogs and cats that present with AKI (68). We have become more cognizant to the negative effects of intravenous fluids and will continue to make new discoveries how the kidneys function in a dysfunctional state. As we gather more data in animals with renal injury, the question becomes truly which fluid type is recommended for these animals?

Unfortunately, accurate assessment of animal weight, which is used as a surrogate for fluid status, is challenging, as the body converts to a hypercatabolic state in established AKI and loss of muscle mass. Luckily, providing nutrition and water through an established feeding tube (E-tube, PEG, G-tube) is an ideal way to help manage the catabolism of muscle and daily fluid requirement. Ultimately, the best fluid therapy is one that maintains euvolemia, with the goal of delivering fluid in the most physiologic manner (via the GI tract).

AUTHOR CONTRIBUTIONS

CL and DG contributed to write the manuscript. All authors contributed to the article and approved the submitted version.

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Fluid Therapy in Pulmonary Disease: How Careful Do We Need to Be?

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Intravenous fluid therapy is a vital and life-saving therapeutic in veterinary medicine. In the absence of heart or lung disease, trauma or sepsis there is limited evidence that fluid therapy will have a detrimental effect on lung function. In healthy dogs there is a reasonable level of experimental evidence that supraphysiologic rates of fluid are required before signs of fluid overload are made evident. In cats, however, this may not be the case. There are higher rates of asymptomatic myocardial disease, but even in the absence of that it seems that some cats may be susceptible to fluid overload. Where systemic inflammation already exists the careful homeostatic and protective mechanisms within the lung are deranged and increases in hydrostatic pressure are more likely to result in fluid movement into the lung tissues. Strategies including restricting the use of intravenous crystalloid fluid administration and using blood products for management of severe hemorrhage are of increasing importance in human trauma and seem to be associated with fewer pulmonary complications, and lower mortality. Managing dogs and cats with sepsis and acute respiratory distress syndrome is already challenging, but ensuring adequate vascular expansion needs to be balanced with avoiding excessive volume administration which may negatively impact pulmonary function. While fluids remain crucial to management of these conditions, there will be an ongoing requirement to balance need without providing excess. The use of point of care ultrasound may provide clinicians with a non-invasive and accessible way to do this.

Keywords: crystalloid, colloid, pulmonary oedema, cat, dog

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INTRODUCTION

Fluid therapy is a vital part of the management of the acutely or critically ill veterinary patient. Despite being considered a relatively benign therapy in veterinary practice, emerging evidence in human patients has identified that there is a need for careful fluid balance to avoid excessive morbidity or mortality (1). This effect seems to be most pronounced in the most severely ill people. An association between increased mortality and cumulative fluid balance in people with acute respiratory distress syndrome (ARDS) has been shown (2). In healthy animals the lung is protected against the effects of excessive fluid accumulation. However, in disease where there may be alterations in fluid fluxes, these protective strategies may fail, and excessive fluid administration can significantly affect lung function. This article will discuss normal fluid dynamics in the lungs, the influence of disease on these dynamics, and the potential impact of fluid therapy. The following writings will explore the experimental, human and veterinary clinical evidence specifically related to conditions where fluid therapy and pulmonary dysfunction are of particular concern; trauma and pulmonary contusions, sepsis, systemic

inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS).

FLUID DYNAMICS IN THE LUNG

Fluid dynamics within tissues are complex. In recent years the endothelial glycocalyx has been identified as an important consideration in the formation of extravascular fluid, as well as the forces described by Starling (3, 4). Starling's original model defined the movement of fluids from the semi-permeable intravascular spaces as being subject to intra- and extravascular colloid osmotic pressure (COP) and hydrostatic forces, specifically the gradients formed between these at the arterial and venous ends of the capillary. Starling's model proposed that the majority of fluid extravasation occurring at the arterial end and fluid resorption at the capillary end. In health the glycocalyx, which is a thin matrix of glycoproteins, proteoglycans and glycosaminoglycans on the endothelial (luminal) surface of vells, maintains normal vascular permeability and transvascular fluid movement. The effect of the glycocalyx is that, in contrast with the original Starling model, the COP contributes less of an impact to transvascular fluid flux. In the revised model the COP gradient is generated between the plasma (within the vessel) and the subglyceal space. The COP of the subglyceal space is very low, and the effect of this is that the most relevant COP gradient is between the endothelial surface layer and the subglyceal space rather than the lumen and the subglyceal space. As a result of this fluid extravasation is low and constant along the entire length of the capillary and in contrast with Starling's original model the resorption of fluid is insignificant (5, 6). Damage to the glycocalyx, as measured by increased shedding of glycocalyx biomarkers, occurs in several disease states including trauma and sepsis. It is thought that this damage results in a loss of integrity and increased vascular permeability and fluid flux. It is also thought that subsequent to the loss of glycocalyx the forces described by Starling and in particular hydrostatic pressure, are of greater importance (7). As hydrostatic pressure can be increased through administration of fluid therapy this can potentially promote excessive fluid movement resulting in edema. The loss of the endothelial glycocalyx also results in extravasation of large macromolecules into the interstitium altering the COP gradients and making the most important COP gradient that between the plasma and the interstitial fluid.

In healthy lung tissue there are several additional protective measures that limit the formation of extravascular lung water (EVLW) (8). Capillary hydrostatic pressure can increase without significant leakage into the alveolar tissue. The pulmonary interstitium is non-distensible and limits accumulation of EVLW. This drives any fluid that does accumulate toward the lymphatics which are able to significantly increase flow in response. In addition, the formation of colloid osmotic pressure gradients when fluid transudation does occur ensures that fluid is removed. While these mechanisms function well in health, in diseases where there are alterations in microvascular permeability such as pneumonia or ARDS they are easily overwhelmed. Indeed, once vascular leak has started it is difficult to stop, thus leading to the accumulation of excessive EVLW and pulmonary dysfunction.

FLUID THERAPY AND PULMONARY FUNCTION

When there is pulmonary inflammation or damage to the glycocalyx, fluid therapy affects these delicate relationships by increasing capillary hydrostatic pressure. In these circumstances the result can be overwhelming, resulting in alveolar flooding and pulmonary edema. The impact of fluid therapy and specifically that of the volume, or dose administered, is therefore of most importance in animals where there is endothelial damage or inflammation. There is limited data that supports the formation of non-cardiogenic pulmonary edema in veterinary species as a result of appropriate doses of intravenous fluid in the absence of lung injury or damage. Experimental data in healthy dehydrated dogs examining the dose response effect of lactated Ringer's solution identified that high rates and doses were associated with clinical signs of fluid overload. However, the doses that resulted in side effects associated with fluid overload were between 270 and 360 mL/kg/h administered for an hour, which would not be used in clinical circumstances (9). Furthermore, doses of 135 mL/kg administered for 60 min were not associated with pulmonary dysfunction when given under experimental conditions in dogs (10).

In veterinary patients, fluids are used for management of several conditions. In the acute situation intravenous fluids are used most commonly for management of intravascular fluid deficits (11). Management of intravascular volume deficits (hypovolemia) typically involves the administration of aliquots (25% of blood volume) of isotonic crystalloid fluids up to a rate of 90 mL/kg/h, which is below the experimental doses reported (11). Recent experimental work in a rat hemorrhage model comparing the effects of a 1:1 blood volume lost to replacement crystalloid ratio with a 1:3 ratio identified increased histologic lung edema scores and wet:dry lung weight, but there was no effect on PaO_2 (12). Despite this, it would seem that clinically, rates used in the acute setting for resuscitation have limited immediate effect on pulmonary function in the absence of pre-existent pulmonary inflammation or injury. In the chronic phase of fluid therapy however, if these drugs are used in inappropriate circumstances, at inappropriate rates or for too long of periods, they will contribute to volume overload and a positive fluid balance. Fluid overload, defined as accumulation of edema secondary to excessive retention of administered fluid, has been identified in critically ill dogs, and has been associated with increased mortality (13). The effect of fluid overload on pulmonary function has not been evaluated clinically in dogs and remains an area in which veterinary clinicians are dependent on interpretation of the human and experimental literature. Fluid overload resulting in pulmonary dysfunction has, however, been described in a population of cats with urethral obstruction (14). In this population, heart disease (hypertrophic cardiomyopathy and hypertrophic obstructive cardiomyopathy) was identified in most of the cats (83%) in which cardiac evaluation was

performed. Administration of a fluid bolus was also identified as a risk factor for fluid overload (14). As a proportion of cats will not have easily identifiable signs of myocardial disease on clinical examination (15) cats are at particular risk of fluid overload. However, it appears that clinically, even cats without heart disease are more susceptible to the pulmonary effects of fluid therapy and so extra care needs to be taken in this species.

When considering the impact of fluid therapy on pulmonary function for an individual patient, it is important to first identify the reasons for administration of fluid and know which measures you can be used to monitor effectiveness of the fluid administered. Secondly, it is important to have methods for monitoring for the development of pulmonary dysfunction and pulmonary edema. Methods for assessment of fluid requirements are poorly evaluated in the veterinary literature. We are currently reliant on physical examination, calculated indices such as shock index and biomarkers, such as lactate to identify significant hypoperfusion (16, 17). There is increasing focus on the use of point-of-care ultrasound to provide more objective measures which can be used alongside other indicators to improve and refine our approach to this (18, 19).

Pulmonary function can be monitored subjectively through the use of physical examination and using subjective measures such as pulse oximetry (more useful in anesthetised patients) or arterial blood gas analysis. Assessment for pulmonary edema can be more challenging. Techniques that measure EVLW are not available in clinical veterinary practice and are invasive. Thoracic imaging, including radiography and ultrasound are easily available and generally non-invasive. Assessing animals for the development of pulmonary edema during clinical care has been improved by the advent of point-of-care ultrasound. Several studies evaluating the use of focussed protocols for lung ultrasound have been published in veterinary medicine (20–22). This technique has also been shown to be valuable in dogs without radiographic changes (20). Identification of pulmonary infiltrates is relatively easy with minimal training and allows bedside, non-invasive assessment of cats and dogs that are considered at risk of development of pulmonary edema (23). Good correlation has been shown between the presence of B-lines and extra-vascular lung water in critically ill human patients (24). B-lines are comet tail artifacts that are visible on ultrasound of the lung tissue. They are hyperechoic, well-defined and should move synchronously with lung sliding. Less than 3 B-lines/field of view is considered normal. The use of the described lung ultrasound protocols ensures full evaluation of the lungs and therefore understanding of whether B-lines, if present, are diffuse or focal. Diffuse B-lines would be suggestive of pulmonary edema, particularly if acute in origin. Other differentials for diffuse B-lines include pulmonary fibrosis. Focal B-lines may indicate focal consolidation due to pneumonia, hemorrhage or contusion. While the published veterinary literature currently focusses on the use of detection of B-lines in dogs and cats with pulmonary edema secondary to congestive cardiac failure, there is no reason while the same ultrasonographic approach cannot be used for the monitoring of patients at risk of non-cardiogenic pulmonary edema.

PULMONARY EFFECTS OF FLUID THERAPY IN TRAUMA AND LUNG CONTUSIONS

The detrimental effects of intravenous fluid therapy on lung contusions have been known for over 60 years (25). An association between high volumes of fluid following trauma and mortality was identified nearly 30 years ago, although causation was not shown (26). Resuscitation in trauma remains controversial in human patients and is an area of active research. More recently there has been increased focus on the use of blood products for definitive volume replacement, particularly when there is massive blood loss (27).

Experimental studies in pigs in a model of blunt lung injury have confirmed a relationship between increased lung water and administration of crystalloid or artificial colloid solutions, with variable clinical effects (28–31). In these studies, use of crystalloid solutions were associated with increased lung water compared with colloid/crystalloid mixtures.

In an older animal model of lung contusion and hemorrhage the infusion rate of Ringer's lactate solution used for resuscitation was directly related to the degree of pulmonary insufficiency identified (31). Clinically relevant rates of 60–90 ml/kg/h were included in this study. However, rates of up to 30 mL/kg/h for a maximum of 3 h had limited effects on lung function (31). The utility of these experimental studies is questionable due to short follow up times, the cause of injury and controlled nature of the studies (28–31). However, they point toward a link between increased volumes of crystalloid administration and increased EVLW and potentially pulmonary dysfunction (28–31).

Large multi-center clinical studies in people have also identified an association between severity of hypoxemia and the volume of crystalloid administered, particularly if administered within the first 6 h following arrival at the hospital (32). Furthermore, in severely injured people predicted to require massive transfusion, an association between the development of ARDS and number of 500 mL isotonic crystalloid boluses was identified, which was independent of the volume of blood products administered. In this population, patients developing ARDS received a mean of 12 × 500 mL (total 6 liters) boluses compared with 8 × 500 mL (total 4 liters) boluses in the group that did not develop ARDS (33). In an average 70 kg person this represents a difference between 85 and 57 mL/kg. In severely injured people presenting with significant blood loss, administration of blood products during resuscitation is associated with lower mortality (34) and the current focus is on restriction of crystalloids following admission.

Applying this evidence to veterinary patients is challenging. Our patient population generally has less significant injury, or potentially our capability to manage severe injury is less than in human medicine. Availability of large volumes of blood products is also more limited in all but the largest hospitals. However, current evidence supports the use of restricted volumes of crystalloid at rates of <30 mL/kg/h to limit pulmonary effects, while ensuring adequate resuscitation using physical

examination markers of perfusion, lactate concentrations and other markers of perfusion. When there is severe hemorrhage requiring fluids for resuscitation, the use of blood products instead of non-sanguineous fluids is justified where possible.

PULMONARY EFFECTS OF FLUID THERAPY IN SEPSIS, SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, AND ACUTE RESPIRATORY DISTRESS SYNDROME

Fluid therapy in human sepsis is a very controversial topic despite decades of research. Following the publication of improved outcomes with early goal directed therapy large volumes of fluid were recommended to target specific blood pressure and central venous pressure end-points (35). However, a recent metanalysis did not identify mortality differences between lower and higher fluid volumes in the initial management of sepsis (36). Notably a study in African children with sepsis showed that a more restrictive fluid administration protocol resulted in improved survival (37). Perhaps not surprisingly, as sepsis is the main cause of ARDS in people (38), much of the clinical literature examining effects of the pulmonary function in critically ill human patients examines it through the lens of ARDS. Differentiation of ARDS from other causes of pulmonary edema can be challenging clinically (39). In people and veterinary species ARDS is caused by increased pulmonary capillary permeability secondary to inflammation and is defined as the presence of bilateral lung infiltrates in the absence of systolic heart failure or fluid overload. Acute respiratory distress syndrome is associated with increased EVLW, and the alveolar fluid that accumulates is typically protein rich. As there is increased pulmonary capillary leak in ARDS it follows that increases in capillary hydrostatic pressure will result in worsening of fluid accumulation. Pulmonary edema caused by left sided congestive cardiac failure (i.e., circulatory volume overload) is a contraindication for intravenous fluid therapy and will not be further discussed in this article.

In an experimental pig model of sepsis resuscitation with large volumes of fluid in early sepsis did not result in increased EVLW (40). Similarly in a recent retrospective study in people with sepsis who received a minimum of 30 mL/kg isotonic crystalloid fluid for resuscitation, administration of 30 mL/kg within the first 2 h, compared with lower rates of administration did not result in increased rates or duration of mechanical ventilation (40). Interestingly in this population the percentage of patients requiring mechanical ventilation was significantly lower in patients receiving the higher rates of fluid administration (0.25–0.5 mL/kg/min) (41). When specifically examining a small cohort of critically ill people that develop ARDS, a significant role for the volume of fluid administered intraoperatively has been identified, with patients receiving >20 mL/kg/h having 3.8 times higher adjusted odds of developing ARDS compared with those that received <10 mL/kg/h (42). In contrast to this, when examining risk factors for development of pulmonary edema following fluid loading in critically ill patients, relatively high baseline cardiac index and pulmonary vascular filling were found to be more important than pulmonary vascular permeability and filling pressures or volume of fluid administered (43). It was thought that these indicated a plateau in cardiac function and an inability to cope with the fluid volume administered. These effects are demonstrated in **Figure 1**. Even with normal permeability, when volume expansion reaches a critical point, extra-vascular lung water increases. In ARDS patients who have altered vascular permeability, these changes are seen at lower filling pressures (lesser volume expansion). In addition to volume of fluid administered, the presence of sepsis and volume of fluid administered was not found to be predictive of formation of pulmonary edema in this latter study. Although the results of these two studies may seem conflicting, one is retrospective examining patients presenting with ARDS to an ICU, and one prospective, primarily designed to examine the effect of fluid types on EVLW /pulmonary edema formation rather than the mechanisms. The studies were also measured over different time courses. In the former study the mean time to the development of ARDS was 2.6 days, whereas in the latter study pulmonary edema was inferred from increased EVLW during the course of fluid administration. It would seem therefore that in the acute setting cardiac function is more important for the formation of pulmonary edema, but that high volumes of fluid administered intraoperatively may impact on the development of ARDS.

Once ARDS is present, the management of fluid therapy becomes complex. As seen previously, many patients with ARDS have sepsis, and management of sepsis typically requires administration of intravenous fluids to maintain homeostasis. Assessing fluid requirements, responsiveness and balance is of particular challenge in these patients and an area of active research. Given that ARDS is a form of non-cardiogenic pulmonary edema associated with alterations to pulmonary vascular permeability, it makes biological sense to limit increases in hydrostatic pressure to minimize further worsening of pulmonary function. Restrictive fluid therapy strategies in ARDS are supported by several retrospective studies (45–47). A large prospective study comparing a restrictive and liberal fluid therapy approach in patients with acute lung injury (now included within the definitions of ARDS) demonstrated that the restrictive group had more ventilator free days and better lung function than the liberal group although there was no difference in outcome (48). Management of ARDS is challenging in veterinary patients, and as prolonged ventilation is both difficult and expensive how veterinarians apply the human literature in this area needs careful consideration. Avoiding deterioration of lung function is of great importance, and lessons from the human literature highlight the use of carefully balanced fluid therapy, to ensure adequate tissue perfusion while avoiding fluid overload. Clinically dogs with pneumonia may have sepsis and are at risk of ARDS (49). Pneumonia by definition represents inflammation of the lung tissue and will therefore result in alterations in fluid dynamics within the lung. It is this cohort of patients that pose the greatest challenge to veterinary clinicians, as managing their fluid requirements may impact their pulmonary function.

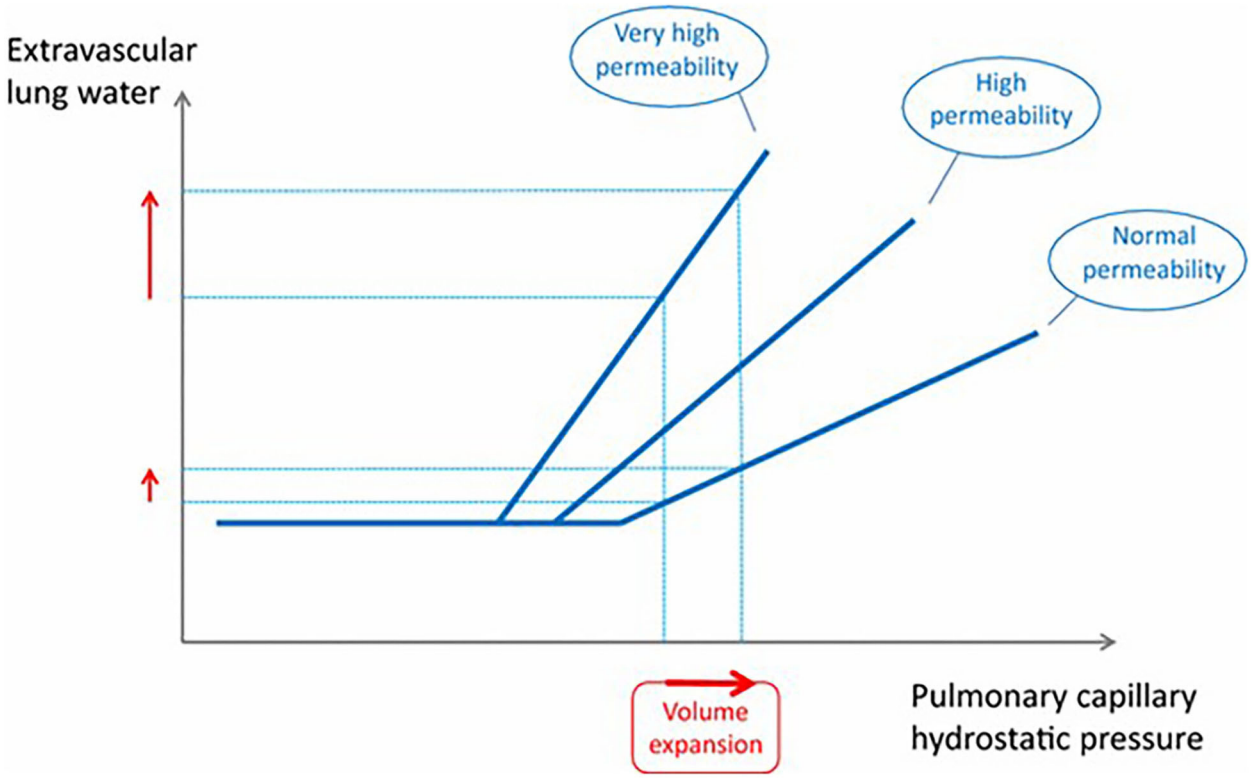

FIGURE 1 | This graph shows the relationship between pulmonary capillary hydrostatic pressure and extravascular lung water. Beyond a certain point continued volume expansion results in increased extravascular lung water, an effect that is more pronounced when lung permeability is increased. From Jozwiak et al. (44).

DISCUSSION

Intravenous fluid therapy is a vital and life-saving therapeutic in veterinary medicine. The evidence supporting a detrimental impact of fluid therapy on lung function is limited to disease states. The effects of excessive fluid therapy in animals with known cardiac disease is well-known. In addition to this, animals that have suffered trauma, have sepsis or inflammatory lung disease should be considered at risk of deteriorating lung function as a result of overzealous fluid therapy after initial resuscitation.

The effects of fluid overload in healthy animals usually only occur in supraphysiological doses, however due to their smaller blood volume and increased incidence of undiagnosed or asymptomatic myocardial disease, extra caution is required in cats.

In sick animals the impact of the underlying condition should be considered as this may impact on the fluid therapy plan and influence monitoring.

There is clear evidence in the literature that limiting fluid rates in people with trauma is important to prevent respiratory complications. In patients with sepsis the data is more difficult to interpret. Restoration of perfusion is of critical importance, and in patients that are fluid deplete administration of intravenous fluid therapy is important, but overload must be avoided. Early use of vasopressors is increasingly promoted in people with sepsis to avoid fluid overload. The importance of this in veterinary species is unknown, and clinical experience suggests that fluid deficits are common in these patients. Assessing whether fluid deficit is present is potentially challenging, but the use of point-of-care ultrasound using for example, measurements of the caudal vena cava is allowing more careful and individualized patient care. In addition, the use of monitoring tools such as body weight, serial physical examination, urine output and specific gravity allows individualized patient care and may improve prescription of fluid therapy.

While management of these animals will remain challenging when formulating individualized and flexible fluid therapy plans, using phased approaches, e.g., ROSE approach (resuscitation, optimization, stabilization, and evacuation) will allow veterinary clincians to limit any potentially detrimental effects.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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Fluid Resuscitation for Refractory Hypotension

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Hypotension is a common occurrence, especially in anesthetized patients and in critical patients suffering from hypovolemia due to shock and sepsis. Hypotension can also occur in normovolemic animals, anesthetized or conscious, under conditions of vasodilation or decreased cardiac function. The main consequence of hypotension is decreased organ perfusion and tissue injury/dysfunction. In the human literature there is no consensus on what is the threshold value for hypotension, and ranges from < 80 to < 100 mmHg for systolic blood pressure and from < 50 to < 70 mmHg for mean arterial blood pressure have been referenced for intraoperative hypotension. In veterinary medicine, similar values are referenced, despite marked differences in normal arterial blood pressure between species and with respect to humans. Therapeutic intervention involves fluid therapy to normalize volemia and use of sympathomimetics to enhance cardiac function and regulate peripheral vascular resistance. Despite these therapeutic measures, there is a subset of patients that are seemingly refractory and exhibit persistent hypotension. This review covers the physiological aspects that govern arterial blood pressure control and blood flow to tissues/organs, the pathophysiological mechanisms involved in hypotension and refractory hypotension, and therapeutic considerations and expectations that include proper interpretation of cardiovascular parameters, fluid recommendations and therapy rates, use of sympathomimetics and vasopressors, and newer approaches derived from the human literature.

Keywords: anesthesia, cardiac output, hypotension, sepsis, vasodilation

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INTRODUCTION

What Is Hypotension?

In simple terms, hypotension is a lower than normal arterial blood pressure. However, this definition does not imply when and at what specific values is hypotension harmful to the patient. Hypotension is a common occurrence, especially in anesthetized animals and in critical patients suffering from hypovolemia due to shock and sepsis.

Mean arterial blood pressure values of 60 mmHg or less and systolic arterial blood pressure values of 80 mmHg or less have been reported as indicative of excessive hypotension in animals, and ideally these pressures should be maintain above 80 mmHg and 100 mmHg for mean and systolic arterial blood pressure, respectively (1). However, arterial blood pressure values vary among species (**Table 1**), so the use of a common value as the threshold value for all species is not accurate and is best to keep in mind specific species values during the assessment of low arterial blood pressures. In addition, arterial blood pressure is consistently lower in the anesthetized than in conscious patients.

In humans, where studies have been completed with sufficient statistical power, there is still no

TABLE 1 | Normal arterial blood pressure (mmHg) and cardiac index (mL/kg/min) in different species.

	Conscious				References
	Systolic	Diastolic	Mean	Cardiac index	
Human	120	80	93	71–86	(2)
Dog	150	98	115	165	(3, 4)
Cat	108–120	79–87	92–103	200	(5, 6)
	130–151	94–115	113–140	NR	(7)
	NR	NR	142–165	NR	(8)
Horse	147	92	115	60	(9)
	163	100	125	79	(10)
Cattle	155	105	123	119	(11)
Sheep	125	96	109	144	(11)
Goat	105	70	86	132	(11)
Rabbit	100	65	75	104–237	(12–15)

NR, not reported.

consensus on what is the threshold value for hypotension to provide a widely accepted definition (16–18) and this is further complicated when adults are compared to pediatric patients (19) because arterial blood pressure is consistently lower in the latter population.

ARTERIAL BLOOD PRESSURE

Physiology for Arterial Blood Pressure Control

The major function of the nervous system on the circulatory system is to control arterial blood pressure by allowing adequate and independent blood flow to the individual needs of tissues and organs, and regardless of the amount of blood that flows to any given tissue, arterial blood pressure remains constant (20).

Arterial blood pressure control is necessary for short- and long-term situations, and it differs between. Short-term refers to acute changes (usually minutes to hours), whereas long-term refers to chronic changes (hours to weeks). Short-term control occurs through changes that affect both cardiac output and arterial blood pressure, and include variations in vascular resistance and compliance, contractility, heart rate and blood volume (**Figure 1**) (20). An example of short-term control are changes that occur during exercise in all or most of the factors (resistance, compliance, contractility, heart rate), to increase arterial blood pressure and cardiac output to meet tissue demands, but the increase in cardiac output exceeds that of arterial blood pressure because local muscle activity results in a decrease in vascular resistance (vasodilation) to improve blood flow while veins and small arterioles of other tissues exhibit a decrease in vascular compliance (constriction) to improve venous return (20). If arterial blood pressure and cardiac output do not meet tissue demands, there is less provision of nutrients and oxygen and the onset of anaerobic activity (21).

Individually, each of these factors result in specific changes in arterial blood pressure and/or cardiac output; however, with an intact nervous system it is the interaction between factors that determines the final cardiovascular effect. In simple terms, Ohm's Law [electrical current (I) through a conductor is proportional to voltage (V) and inversely proportional to resistance (R), ($I = V \div R$)] can be used to define the interaction between arterial blood pressure and cardiac output, where I is equivalent to cardiac output (CO), V is arterial blood pressure (ABP), and R is vascular resistance (VR), so that $CO = ABP \div VR$. For example, vascular resistance on its own can affect arterial blood pressure and cardiac output in opposite ways, a decrease in vascular resistance lowers arterial blood pressure and could increase cardiac output, whereas an increase in vascular resistance results in higher arterial blood pressure and limits cardiac output (20).

Volume administration increases cardiac output by increasing preload, and can potentially increase arterial blood pressure if the nervous system does not exert a reflex control over vascular resistance. This effect of volume administration without a change in arterial blood pressure is notable in conditions of normovolemia, where an increase in circulating volume results in a decrease in vascular resistance (20, 22, 23) and the compliance of the vascular system and tissues can store a significant volume, blunting any change in circulating volume (20, 22–25). If the decrease in vascular resistance was prevented during fluid administration in a normovolemic patient with a vasoconstrictor, then arterial blood pressure could also increase in conjunction with cardiac output (20). This is often observed with use of alpha-adrenergic drugs (vasoconstriction) but only if contractility can overcome the increase in vascular resistance (afterload) (26–29). The benefits of volume administration to increase arterial blood pressure are obvious in conditions where there is an ongoing deficit in circulating volume (hypovolemia).

An increase in heart rate can result in an increase in cardiac output and arterial blood pressure, but only if the circulating volume is ideal. A low circulating volume (hypovolemia) results in low venous return (preload) and a low right atrial pressure, even below 0 mmHg. The veins entering the chest will collapse with subatmospheric pressures and without proper preload the cardiac output and arterial blood pressure do not benefit from an increase in heart rate (20). Conversely, if preload is increased, an increase in heart rate is beneficial to cardiac output and arterial blood pressure, because it helps eject effectively the returning blood back into the circulation. However, an excessive increase in heart rate is not beneficial because diastolic time is shortened and decreases stroke volume, in addition to increasing the work of the heart, which weakens the heart contractility, all of which affect cardiac output negatively.

Long-term control of cardiac output and arterial blood pressure is the result of adaptation of baroreceptors within hours to days to changes in circulating volume and arterial blood pressure, of the instauration of higher vascular resistance that results in higher arterial blood pressure and minimal changes in cardiac output, and of an active participation of the kidney that responds to the increase in arterial blood pressure with endocrine and electrolyte mechanisms to control pressure and volume by increasing urinary output (20).

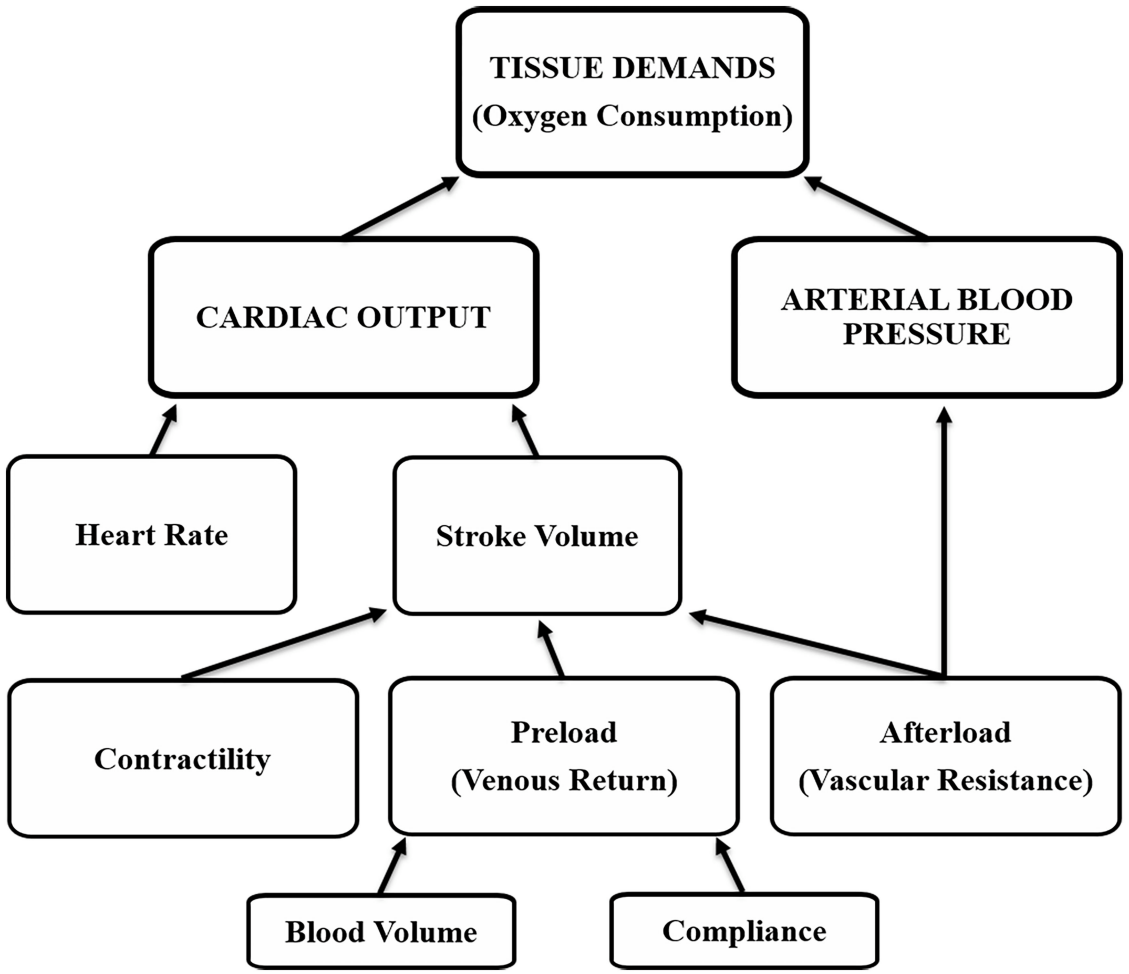

FIGURE 1 | Tissue oxygen demands are met by cardiovascular factors that affect cardiac output and arterial blood pressure.

Hypotension and Tissue Perfusion

Hypotension has been associated with decreased organ perfusion and injury/dysfunction, which in humans may include myocardial infarction (17, 30, 31), acute kidney injury (17, 31–34) and increased mortality (30, 35).

In general, most studies in humans have associated mean arterial blood pressures of $\leq$ 55 mmHg with adverse cardiac- and renal-related outcomes, and the duration of the hypotensive episode increases the risk of that adverse outcome (17, 18, 31, 34). Even at mean arterial blood pressures just $<$ 80 mmHg, a hypotensive episode of more than 10 min can increase the risk of organ injury, and at lower pressures, less time is required for increased risk (18). Interestingly, improving cardiac index by 21% and mean arterial blood pressure from 65 to 85 mmHg with norepinephrine in septic human patients did not result in better renal function than in patients kept at the lower arterial blood pressure and cardiac index (36); likewise, in research dogs, acepromazine intramuscular administration as premedication resulted in a mean arterial blood pressure of 66 mmHg due to its vasodilatory effects, during isoflurane anesthesia for 2.25 h, lower than pressures in the same dogs after saline administration (87 mmHg), but creatinine levels, ALP-creatinine ratio in urine, and renal blood flow and glomerular filtration rate (GFR) assessed with scintigraphy were similar and within normal ranges in both groups (37).

Several aspects need to be considered to interpret hypotension. First of all, the threshold value for hypotension should not be generalized between conscious and anesthetized patients, since as stated before, values differed in the two situations and values also differ between species. A patient positioned in recumbency (dorsal, ventral, lateral) position, as it happens during anesthesia, offers the heart ideal work conditions because the effect of gravity is reduced by leveling all organs and tissues with the heart, and therefore changes to increase vascular resistance become less necessary in stable patients. In the standing position, gravitational forces result in lower pressures in the upper part of the body and higher pressures in the lower part of the body, which is counteracted by an increase

in arterial vascular resistance and pulse rate, so that mean arterial blood pressure remains constant or slightly elevated throughout the body (38). In addition, in the standing patient, cardiac output decreases due to the increase in vascular resistance, and tissues can have a reduction in blood flow, including the kidney, which decreases GFR and increases arginine vasopressin (antidiuretic hormone) (38). General inhalant anesthesia and recumbency usually results in vasodilation and a decrease in vascular resistance, which helps maintain cardiac output if contractility is adequate, despite the reduction in mean arterial blood pressure. This could help explain why despite low mean arterial blood pressure in anesthetized patients, renal blood flow and function can remain normal in some studies (36, 37). Furthermore, the additional decrease in vascular resistance caused by drugs like acepromazine due to its alpha-blockade, allows for GFR and renal blood flow to be maintained within normal limits during general anesthesia, unlike conscious dogs maintained in lateral recumbency, where mean arterial blood pressures of < 80 mmHg decreased GFR but not renal blood flow, which was also impaired if mean arterial blood pressure was < 66 mmHg (39). These studies demonstrate that if the decrease in mean arterial blood pressure is the result of a decrease in vascular resistance, while contractility (cardiac output) is acceptable, an anesthetized patient can tolerate these pressures if not excessively low or for too long, and maintain adequate blood flow to tissues for their normal function.

It is also difficult to conclude when hypotension is significant enough to result in an adverse outcome, which is further confounded by how hypotension is defined in any study. Findings from different studies cannot be generalized because small changes in the selected threshold values for hypotension among human studies can result in wide differences in the incidence of intraoperative hypotension (5–99%) and do not necessarily reflect organ dysfunction as a consequence of hypotension (16). More importantly, the variation in adverse outcomes as it relates to hypotension can be explained in part by the health status of the patient [American Society of Anesthesiologists (ASA) classification] and whether pre-existing hypovolemia or cardiac disease are the primary causes, since morbidities and mortality are associated with older age and higher ASA status risk in human patients (17, 18, 30, 31, 33, 35).

Studies in healthy dogs and foals under research conditions, where hypotension was induced by deep anesthesia with inhalant anesthetics in normovolemic conditions, resulted in no adverse outcomes despite mean arterial blood pressures of 24 mmHg for at least 15 min in foals (26) and 46 mmHg for at least 45 min in dogs (23), although pressures were normalized in those animals before recovery from anesthesia.

REFRACTORY HYPOTENSION

Hypotension that persists, despite appropriate therapeutic measures that consistently correct it, probably exhibit refractory hypotension. Refractory hypotension is most commonly encountered under conditions of shock due to hypovolemia or sepsis, but can also include cardiogenic, neurogenic, and anaphylactic shock (40). Refractory hypotension and shock develops in nearly 6% of critically ill human patients (41) and mortality rates are usually > 40–50% because of progressive hypotension (42, 43).

Hypovolemic Shock

Hypovolemic (hemorrhagic) shock is due to a reduced intravascular volume (preload), which results in low cardiac output and arterial blood pressure. In human medicine hypovolemic shock is rated into four classes, from least to most critical, according to the "Advanced Trauma Life Support (ATLS®)" guidelines of the American College of Surgeons. The patient is allocated to one of the classes according to degree of blood loss (< 15% in Class I, 15–30% in Class II, 30–40% in Class III, and > 40% in Class IV) and degree of alteration of vital signs, including pulse rate, blood pressure, pulse pressure, respiratory rate, mental status, and urinary output (44). However, not every trauma patient fits the description of any single class and only in classes III and IV is hypotension a clinical sign (44).

In conscious, splenectomized research dogs, removal of 43 mL/kg of blood [53% of blood volume; (45)] in 10 min resulted in an immediate drop in mean arterial blood pressure from 106 mmHg to 25 mmHg and a gradual recovery over 72 min to a decompensated mean arterial blood pressure of 61 mmHg (46). During this period, dogs were untreated and heart rate increased from 81 beats/min before hemorrhage to over 186 beats/min, and both plasma total protein and packed cell volume decreased. Over the next hour, mean arterial blood pressure decreased again to the initial drop and heart rate was over 220 beats/min, to which the dogs succumbed to death (46).

The response to blood loss is different under conditions of general anesthesia, both with inhalant and injectable anesthetics, because these drugs inhibit, in a dose-dependent fashion, baroreceptor reflex and sympathetic activity, which interferes with normal short-term control (47–49). In addition, blood loss in itself results in decreased requirements of inhalant anesthetics (50), which deems the patient at a deeper level of anesthesia during the hypovolemic episode and further inhibits any sympathetic response. In anesthetized research dogs, maintained at an end-tidal isoflurane concentration of 1.27 to 1.74% [∼1.0–1.3 times the minimum alveolar concentration (MAC)] to induce a mean arterial blood pressure to 65 mmHg, removal of ∼25 mL/kg of blood (31% of blood volume) over 30 min resulted in inhalant anesthetic dose-dependent effects: no change in arterial pressure with lighter anesthesia to a drop to 45 mmHg with deeper anesthesia, heart rate can remain unchanged or increase slightly with lighter anesthesia and decrease slightly with deeper anesthesia, cardiac index and stroke volume may not change with lighter anesthesia and decrease with deeper anesthesia, systemic vascular resistance not change or increase slightly, and total protein and packed cell volume had not changed with the bleeding (51, 52). A similar blood loss of 30 mL/kg in one study decreased MAC by 16% (50) and it is likely that some of the observed changes are also influenced by the increased MAC multiple (if MAC decreases by 16% and the end-tidal inhalant concentration is not adjusted, MAC becomes 1.16% higher); therefore, under clinical conditions is important

to consider adjusting the anesthetic plane during hemorrhage to avoid the contribution of a higher MAC multiple on blood loss and its negative effect on the inhibition of baroreflexes and sympathetic activity (53).

Septic Shock

Septic shock is discussed in depth in the chapter "Fluid Therapy in Dogs and Cats with Sepsis." In brief, septic shock is a type of distributive shock, in which infection results in organ dysfunction due to a dysregulated response from the patient that results in injury to its own tissues and organs (43). Patients with sepsis exhibit hypotension due to peripheral vasodilation, so septic shock is also known as vasodilatory shock or a state of vasoplegia, and is the most common form of shock encountered in intensive care units (43, 54). The pathophysiological mechanisms, responsible for vasoplegia and decrease vascular responsiveness in septic shock, result in refractory hypotension and are also common to hypovolemic shock, cardiogenic shock and anaphylactic shock (40).

According to the latest consensus for sepsis and septic shock in humans (Sepsis 3.0), patients clinically exhibit persistent hypotension that requires of vasopressors to maintain a mean arterial blood pressure $\geq$ 65 mmHg and a serum lactate level $>$ 2 mmol/L, despite adequate volume resuscitation and the absence of hypovolemia (43). In addition, despite adequate tissue perfusion achieved with ideal mean arterial blood pressure and normovolemia, cells undergo conditions of dysoxia (i.e., inability to match oxygen demand with oxygen supply), which results in organ dysfunction and high lactate levels and results in mortality rates in excess of 40% in human patients (43) and veterinary patients (55–64).

Mechanisms Responsible for Refractory Hypotension

The vasodilation that results from sepsis is the result of several factors that enhance vasodilatory- and inhibit vasoconstrictor mechanisms. These include an unregulated synthesis of nitric oxide, a potent vasodilator, in response to cytokines released during septic and hemorrhagic shock. In dogs with septic peritonitis, levels of the inflammatory cytokines C-C motif chemokine ligand 2 (CCL2) and interleukin 6 (IL-6) were significantly higher than in non-septic dogs (64), which contributes to migration and infiltration of macrophages into the area of insult (65). Nitric oxide is produced from L-arginine by nitric oxide synthase, present in endothelial cells, and diffuses into the underlying smooth muscle to activate soluble guanylate cyclase and cGMP production that dephosphorylates myosin, via the myosin light chain phosphatase, causing vasorelaxation (54, 66, 67).

Another mechanism is the result of conditions of local acidosis, with hydrogen ions and lactic acid production from anaerobic metabolism (43, 56, 60, 64, 68, 69). These conditions result in opening of ATP-sensitive potassium channels present in the plasma membrane of vascular smooth muscle and allow an efflux of potassium that hyperpolarizes the plasma membrane and prevents calcium from entering the cell; without intracellular calcium, the phosphorylation of myosin is prevented and the smooth muscle does not contract (54, 66, 70). Metabolic acidosis also promotes overproduction of nitric oxide (70).

The prostaglandin prostacyclin is found in increased concentrations in conditions of septic shock (71). Prostacyclin forms from arachidonic acid from the vascular endothelium by the actions of the cyclooxygenase enzymes and prostacyclin synthase, and once formed it binds to the prostacyclin receptor (IP) and acts on a G-protein coupled receptor which activates adenyl cyclase and stimulates the formation of c-AMP from ATP, which activates protein kinase A and prevents increases in cytoplasmic Ca^{2+}, preventing vasoconstriction and resulting in vasodilation (67).

A final mechanism involves depletion of vasopressin reserves from the neurohypophysis (66). Vasopressin is a potent vasoconstrictor by acting on vasopressin-type 1a receptors (V_{1a}) present in vascular smooth muscle and helps with short-term control of arterial blood pressure under conditions of hemorrhage or sepsis, but this process requires of high circulating concentrations of vasopressin that depletes the stores within 1-h under conditions of profound baroreflex stimulation (54, 66). Interestingly, vasopressin concentrations required for its antidiuretic effect are much lower and still effective under conditions of shock (66).

TREATMENT

The most important step to treat refractory hypotension is to determine the primary cause(s). These include two main reasons, hypovolemia and/or sepsis, and within them the whole spectrum of possibilities, from blood loss, dehydration, sympathetic inactivity or inability to respond, metabolic acidosis, and endotoxemia. Sepsis however, is the most common cause of refractory hypotension due to the vasodilatory effects that result from it (42, 43, 54). The aim of treatment is to overcome the vasodilation that results in hypotension, which is common to classes III ($>$ 30–40% blood loss) and IV ($>$ 40%) of shock (44). An algorithm is provided (**Figure 2**) to help in the decision process during treatment, with an emphasis on short-term control by manipulation of the factors that influence cardiac output and arterial blood pressure, including vascular resistance and compliance, contractility, heart rate and blood volume.

Monitoring of cardiovascular function to assess the condition of the patient and response to treatment is primordial. Arterial blood pressure is readily monitored by non-invasive methods; unfortunately they are inaccurate and unreliable in hypotensive patients (73). Direct arterial blood pressure monitoring is often pursued in critical patients, especially if under general anesthesia, and provides accurate values that can be continuously monitored to assess the effectiveness of fluid therapy when used with dynamic cardiovascular variables such as pulse pressure variation, stroke volume variation and systolic pressure variation, to better define fluid- responsive from non-responsive patients (see chapter "What are the most effective methods for monitoring IV fluid therapy?").

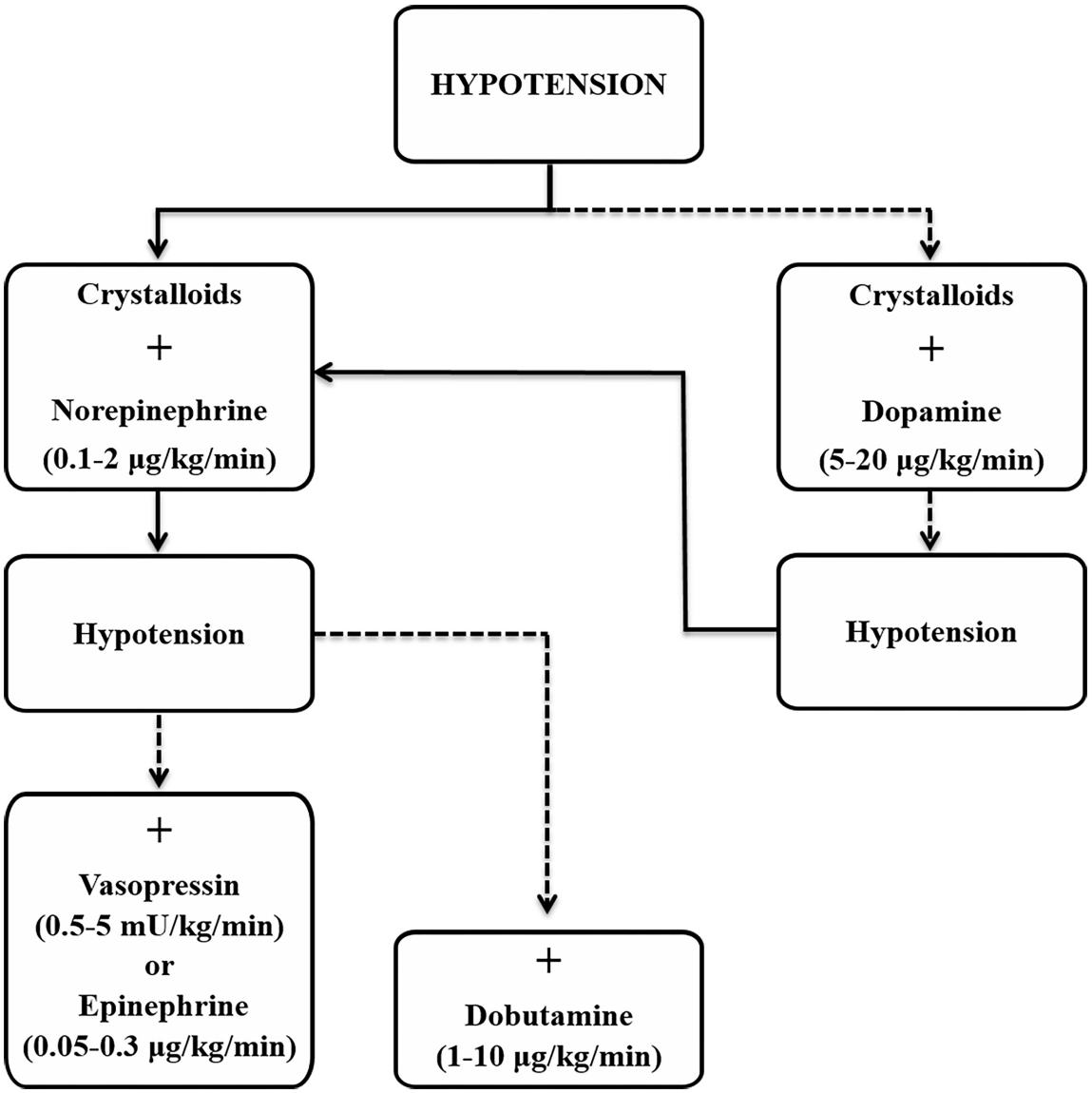

FIGURE 2 | Suggested approach for the treatment of hypotension based on current guidelines for management of sepsis and septic shock (72). Solid line, strong and preferred recommendation; dashed line, weaker recommendation.

Vasopressors

This review starts with vasopressors as the first line of therapy since the basic pathology is the decrease in vascular resistance. However, a combination of at least vasopressors and fluids should be instituted simultaneously for better success in improving arterial blood pressure. The most recent guidelines for management of sepsis and septic shock in people, from 2016, recommends an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors (72).

Vasopressor therapy aims at improving tissue perfusion through vasoconstriction and improved contractility. Norepinephrine, dopamine, epinephrine and phenylephrine are catecholamines used for their vasoconstrictor actions through the alpha-1 receptor, and inotropic actions through the beta-1 receptor, except for phenylephrine that lacks the latter. Arginine vasopressin (vasopressin) is also used for its vasoconstrictor effects, through its V_{1a} receptor action.

Vasoconstrictor actions of alpha-adrenergic drugs on the alpha-1 receptor and of vasopressin on the V_{1a} receptor are linked to G-protein-coupled receptors that result in smooth muscle contraction. Attachment of these agonists to the respective receptors triggers the stimulation of phospholipase C, which generates the production of inositol triphosphate (IP_3) and diacylglycerol (DAG). These two substances interact between them to promote smooth muscle contraction; IP_3 diffuses into the cell to act on an IP_3-sensitive Ca^{2+} channel on the surface of

the endoplasmic reticulum, facilitating the release of Ca^{2+} into the cytoplasm, which stimulates the calmodulin (CM) pathway by forming a Ca^{2+}-CM complex that activates the myosin light-chain kinase and with the presence of ATP, it phosphorylates the myosin light chain and causes vasoconstriction (54). DAG remains in the cell membrane and stimulates the influx of Ca^{2+} into the cytoplasm through a Ca^{2+} channel; this additional Ca^{2+} with the Ca^{2+} released by the actions of IP_3 also stimulates the CM pathway. In addition, the Ca^{2+} from DAG's actions stimulates the janus kinase 2 (JAK2) pathway, responsible for activating rho kinase, which prevents smooth muscle relaxation from occurring by inhibiting the myosin light chain phosphatase, as well as helps release reactive oxygen species, which are useful in increasing the sensitivity to Ca^{2+} and leads to additional stimulation of rho kinase (54).

Inotropic actions of beta-adrenergic drugs on the beta-1 receptor are also linked to G-protein-coupled receptors that trigger the stimulation of adenylyl cyclase to generate the production of cAMP and activates protein kinase A (PKA), which activates L-type Ca^{2+} channels, phospholamban, sarcoplasmic reticulum ryanodine receptor channels (SR), cardiac troponin I (cTnI) and myosin binding protein (MyBP-C) (74, 75). Phospholamban phosphorylation removes its inhibitory effect on SR Ca^{2+} uptake and increases L-type Ca^{2+} current and SR Ca^{2+} cycling to allow for positive inotropic effects, with the contribution of PKA-dependent cTnI phosphorylation (74).

Patients with refractory hypotension under general anesthesia should be supported for contractility through beta-adrenergic inotropic effects because of the vasodilation from inhalant anesthetics and their negative dose-dependent effects on contractility (47, 53). Ideally, a drug with alpha-1 and beta-1 effects should be used to improve both arterial blood pressure and cardiac output, but not at the expense of excessive vasoconstriction that may negatively affect cardiac output. For example, increasing mean arterial pressure to 85 mmHg in patients with septic shock did not improve renal values and metabolic markers (lactate, oxygen consumption) from those already achieved at 65 mmHg (36).

The guidelines for management of sepsis and septic shock have published recommendations on the different types of vasopressors that should be used for resuscitation upon reviewing the literature; the higher the quality of evidence, the more likely a strong recommendation is issued (72). According to the guidelines, norepinephrine is strongly recommended/moderate quality of evidence as the first line-drug (72). Norepinephrine, through its alpha- and beta-1 adrenergic actions, can increase blood pressure and cardiac output (26).

Vasopressin has been considered the second line-drug due to its catecholamine-sparing properties (40, 54). The vasoconstriction and increase in vascular resistance caused by vasopressin can decrease cardiac output (26), and the recent guidelines recommend adding either vasopressin (weak recommendation/moderate quality of evidence) or epinephrine (weak recommendation/low quality of evidence) to norepinephrine to reach the target mean arterial pressure, or adding vasopressin (weak recommendation/moderate quality of evidence) to decrease the norepinephrine dose (72).

Vasopressin due to its actions on V_{1a} receptor does not result in arrhythmias and can increase systemic arterial blood pressure even in the presence of acidemia (76) and has been recommended in refractory shock due to a relative vasopressin deficiency and to benefit from a norepinephrine-sparing effect (40, 77). However, vasopressin can compromise splanchnic and peripheral tissue perfusion under conditions of hypovolemia and these negative effects should be considered (76).

Other catecholamines have been used according to availability, but both norepinephrine and the non-catecholamine vasopressin are considered superior (40, 72). Epinephrine delays normalization of arterial pH and lactate concentrations from exaggerated aerobic glycolysis through Na^+K^+ ATPase stimulation within the muscles, which may interfere with interpretation of a patient's proper responsiveness to treatment and is likely to indicate anaerobic metabolism (78, 79). The current guidelines for management of sepsis and septic shock do not state a specific recommendation for epinephrine on its own, but added to norepinephrine, despite no difference in mortality rate when compared to norepinephrine, although adverse drug-related events were more common with epinephrine (72). In the previous guidelines from 2012, a weak recommendation / moderate quality of evidence was issued for epinephrine (80).

Dopamine is less efficient at normalizing arterial blood pressure than norepinephrine and it has been associated with arrhythmias than norepinephrine (42), most likely because vasoconstrictor effects of dopamine are achieved with higher infusion rates, which also exacerbate beta-1 adrenergic effects (81). In addition, mortality is higher than in patients receiving norepinephrine (42). Dopamine is recommended by the guidelines for management of sepsis and septic shock as an alternative vasopressor to norepinephrine only in highly selected patients (e.g., low risk of tachyarrhythmias and absolute or relative bradycardia) with a weak recommendation / low quality of evidence (72). There is also a strong recommendation/high quality of evidence against the use of low-dose dopamine for renal protection (72).

Phenylephrine is a pure alpha-1 agonist; therefore only vasoconstriction is expected from it, which may be detrimental in hypovolemic patients that also exhibit a reduction in cardiac output, unless contractility is supported with beta-1 agonists (81). Septic patients treated with phenylephrine had a higher mortality rate than patients treated with norepinephrine (82) and current recommendations from the guidelines for management of sepsis and septic shock state that phenylephrine use should be limited until more research is available (72).

Higher doses of catecholamines and/or vasopressin are usually required in refractory hypotension from a decreased response to endogenous or exogenous vasoactive substances such as angiotensin II and vasopressors (83). Tachyphylaxis occurs with high doses and repetitive exposure to alpha-adrenergic drugs, because the alpha-1 receptors are desensitized and internalized (84).

The use of higher doses results in a higher incidence of adverse effects, including arrhythmias (42, 79). In attempts to modulate individual effects and reduce adverse effects, norepinephrine has also been combined with dobutamine (78, 79). Dobutamine

increases cardiac output through its beta-1 adrenergic effects (inotropy), which increases arterial blood pressure under ideal conditions of vascular tone since it lacks alpha-adrenergic effects (26). The guidelines for management of sepsis and septic shock suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor drugs, under a weak recommendation/low quality of evidence (72).

Terlipressin is a prodrug to its metabolite lysine vasopressin; both are more selective and have a longer action than vasopressin for the V_1 receptor for the specific vasoconstrictor effects, but its use is still under investigation for refractory hypotension (40, 54). Selepressin is another V_1 receptor agonist with a short duration of action, that has demonstrated positive effects in cardiovascular variables and fluid balance to prevent lung edema in an ovine model of septic shock (85) and is currently undergoing investigation.

Standard doses of sympathomimetics and vasopressin used to treat hypotension include 1–10 μg/kg/min for dopamine, 1–10 μg/kg/min for dobutamine, 0.1–2 μg/kg/min for norepinephrine, 0.05–0.1 μg/kg/min for epinephrine, 0.5–2 μg/kg/min for phenylephrine, and 0.3–5 mU/kg/min for vasopressin (81). In human patients with refractory hypotension, higher doses than those mentioned above for each of these drugs are often necessary in attempts to manage their cardiovascular derangement (41, 42, 86); from a prognostic point of view, the need for higher doses of vasopressors is associated with unfavorable outcomes (41, 86).

Fluid Therapy

Isotonic crystalloids are recommended as the initial fluid of choice for shock reversal in septic patients, since the time to reach preset values of mean arterial pressure, central venous oxygen saturation, normalization of lactate levels and discontinuation of vasopressors, was achieved as quickly as in patients resuscitated with a combination of synthetic colloids (hydroxyethyl starch or gelatin) and crystalloids (32, 72, 87, 88). One disadvantage of synthetic colloids is that despite their volume expansion/retention properties, often result in higher incidence of impaired renal function than crystalloids and required volumes of resuscitation are only marginally lower than for crystalloids (32). In addition, using starches, dextrans, albumin, fresh frozen plasma, or gelatins *vs.* crystalloids makes little or no difference in mortality of critically ill patients (87, 88). Isotonic crystalloids also resulted in similar outcomes when compared to hypertonic crystalloids (88).

The guidelines for management of sepsis and septic shock in people recommends fluids as follows: a strong recommendation/moderate quality of evidence for crystalloids; a weak recommendation/low quality evidence for use of either balanced crystalloids or saline; a weak recommendation/low quality of evidence for albumin in addition to crystalloids; a strong recommendation/high quality of evidence against hydroxyethyl starches; and a weak recommendation/low quality of evidence for crystalloids over gelatins (72).

Studies in normovolemic and normotensive dogs, maintained at useful clinical inhalant anesthetic concentrations to allow surgery (1.1–1.25 MAC), arterial blood pressure values and the effects on packed cell volume and total protein were similar in groups receiving no fluid therapy or up to 20 mL/kg/h of isotonic crystalloids (24, 25), because fluid balance dynamics and cardiovascular function are well-preserved in those conditions of light anesthetic planes (89, 90).

In hypotensive models using healthy research dogs that were normovolemic and maintained at a systolic arterial blood pressure of 80 mmHg with a deep level of isoflurane anesthesia [3.1–3.4% end-tidal (2.4–2.8 MAC)], isotonic crystalloids, at fast and high volume infusion rates used for shock of 80 mL/kg for up to 1-h did not improve blood pressure, whereas the colloid hetastarch administered at a rate of 80 mL/kg/h to maximum volume 40 mL/kg, restored systolic pressures to within 10% of baseline values predetermined at 1.6–1.7% (1.3 MAC) in 66% of cases (22). In a similar study, research dogs maintained also at 3% (2.3 MAC), arterial blood pressure did not improve with the administration of isotonic crystalloids also infused at a high volume rate of 60 mL/kg/h for 45 min, until the depth of anesthesia was decreased to 1.6% while the fluid rate continued for another 15 min (23).

Normovolemic patients that exhibit hypotension under general inhalant anesthesia do not have increases in arterial blood pressure with high volume fluid rates of isotonic crystalloids, and are also less responsive to colloids, because the infused volume results in a decrease in systemic vascular resistance (22, 23). Despite the hypotension, cardiac output, lactate, venous and arterial pH, and mixed venous oxygen saturation remained within acceptable levels and arterial blood pressure did not decrease any further in these research models (22, 23). According to Ohm's law (ABP = CO ^{x} VR), arterial blood pressure was maintained as a result of an improvement in cardiac output from the expansion in blood and plasma volume (22, 23). Interestingly, with crystalloid administration and under the conditions of deep anesthesia, heart rate and stroke volume did not change in both studies (22, 23). Since cardiac output is also the product of both (CO = HR ^{x} SV), an increase in myocardial contractility is likely responsible for the improvement in cardiac output, as a result of the expanded circulating volume that decreases viscosity from hemodilution of the packed cell volume and total protein, which in association with the lower vascular resistance facilitates the work of the heart, even if arterial blood pressure does not change (22, 23). In this regard, the guidelines for management of sepsis and septic shock only recommend (strong recommendation/high quality of evidence) red blood cell transfusion if the hemoglobin concentration decreases to $<$ 7.0 g/dL in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (72).

Findings from healthy research dogs should be extrapolated cautiously to patients that suffer from refractory hypotension and shock. The expectations and benefits of fluid therapy in normalizing arterial blood pressure differ in normovolemic *vs.* hypovolemic patients. The effects of anesthetic drugs and depth of anesthesia should also be considered. Hypovolemic, septic patients exhibit refractory hypotension and low cardiac output, resulting in long lasting hypotension and severely compromised tissue perfusion that may become irreversible.

The benefit of fluid therapy in reestablishing cardiovascular variables in hypovolemic septic patients is limited without vasopressors. The use of vasopressors should always accompany fast and high volume rates of isotonic crystalloids in these patients, and should include frequent monitoring for hemodilution and decreases in colloid oncotic pressure, because these patients are likely to have impaired oxygen content and delivery, altered fluid transmembrane dynamics and predisposition to edema, all of which affect tissue integrity (91). The most recent guidelines for management of sepsis and septic shock strongly recommends/low quality of evidence that at least 30 mL/kg of IV isotonic fluids be given within the first 3 h and that frequent reassessment of cardiovascular variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others as available) (72).

Other Drugs

Hydrocortisone

Cortisol released by the hypothalamic–pituitary–adrenal axis is important in mediating vasoconstriction through regulation of vascular smooth muscle sensitivity to the endogenous catecholamines norepinephrine and epinephrine and the hormone angiotensin II, and through regulation of cytokines. Mechanisms involved in restoring vascular tone include an increase in alpha-adrenergic receptor gene expression (92); inhibition of the arachidonic acid cascade (93, 94), preventing prostacyclin formation and its vasodilatory effects (67); genomic inhibition of the nuclear translocation of the transcription factor NF-κB, responsible for expression of pro-inflammatory genes for cytokines and chemokines (95); and inhibition of expression of inducible nitric oxide synthase from endothelial cells, halting nitric oxide production and inhibiting vasodilation (96, 97). Hydrocortisone provides both glucocorticoid and mineralocorticoid coverage.

The current guidelines for management of sepsis and septic shock suggests against the use of IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, IV hydrocortisone at a dose of 200 mg per day is suggested (weak recommendation/low quality of evidence) (72).

In patients receiving corticosteroid therapy for chronic autoimmune or inflammatory diseases and in patients receiving replacement therapy because of chronic primary or secondary adrenal insufficiency, it is important that they continue receiving their current dose of corticosteroids to maintain cardiovascular function, especially if general anesthesia is planned. If the patient exhibits refractory hypotension, supplemental hydrocortisone therapy should be considered.

Angiotensin II

Angiotensin II has been recommended due to its actions on the AT1 receptor, a G-protein-coupled receptor, and stimulates the same transduction pathways as vasopressors through activation of phospholipase C for the generation of IP_3 and DAG and stimulation of the JAK2 pathway (21), all of which result in vasoconstriction, aldosterone secretion and vasopressin release (40).

Angiotensin II was evaluated in a double blind, randomized, controlled trial in patients with vasodilatory shock that were not responsive to high doses of vasopressors (98). In this study, patients receiving angiotensin II in combination with the vasopressor had lower requirements for vasopressors, including norepinephrine, and a higher mean arterial blood pressure than the placebo group receiving only the vasopressor; however, mortality rate and adverse effects were similar between the two groups (98). The dose used in this study for angiotensin II was 20 ng/kg/min for the first 3 h, and it was lowered in many instances due to an improvement in the mean arterial blood pressure (98).

Angiotensin II is not mentioned in the most current guidelines for management of sepsis and septic shock (72) because the study by Khanna et al. (98) is contemporary and was not available.

Methylene Blue

Methylene blue inhibits nitric oxide synthase, preventing the production of nitric oxide and cGMP, therefore vasodilation does not occur (99). *In vitro*, methylene blue also suppresses the production and release of prostacyclin, in both the presence and absence of pro-inflammatory cytokines, in dog renal artery smooth muscle cells, which may also contribute to prevent vasodilation by inhibiting the formation of c-AMP, which normally would prevent cytoplasmic Ca^{2+} from causing vasoconstriction (100).

Methylene blue has been used successfully at decreasing mortality in vasodilatory shock after cardiopulmonary bypass at IV doses of 1–2 mg/kg to counteract refractory hypotension that requires of high inotropic support (99). However, its use in vasodilatory shock due to sepsis is not yet established and is not mentioned in the current guidelines for management of sepsis and septic shock (72).

Alpha-2 Agonists

Sedation is often required in human septic patients. Dexmedetomidine has been used for this purpose and spiked interest due to its central and peripheral actions on sympathetic activity and vascular tone. Dexmedetomidine causes vasoconstriction and an increase in mean arterial pressure through its post-synaptic alpha-1 and−2 adrenergic actions, but it can be used also as an antihypertensive drug due to its presynaptic alpha-2 actions that induce a negative feedback on norepinephrine secretion, which causes hypotension (101). However, in rats induced to septic shock, dexmedetomidine administration increased the response to exogenous norepinephrine (102), indicating that it restores the responsiveness to alpha-1 agonists.

In human patients with septic shock and initially maintained sedated with propofol and remifentanil, while receiving norepinephrine to maintain adequate mean arterial blood pressures, had higher norepinephrine requirements than when dexmedetomidine was used to replace the propofol, and norepinephrine requirements increased again when sedation was switched back to propofol (103).

The use of dexmedetomidine is not mentioned in the current guidelines for management of sepsis and septic shock (72).

In summary, refractory hypotension should be addressed aggressively to reestablish arterial blood pressure control and blood flow to tissues/organs. Therapeutic actions include fluid therapy with the use of sympathomimetics and vasopressors that help overcome or at least minimize the ongoing state of vasoplegia, In anesthetized patients, the vasodilatory effects of inhalant anesthetics contribute to the hypotension and anesthesia time should be reduced if at all possible, as well as consider the use of balanced techniques that could help avoid excessive inhibition of sympathetic activity.

AUTHOR CONTRIBUTIONS

AV: manuscript writing.

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Fluid Therapy During Cardiopulmonary Resuscitation

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Cardiopulmonary arrest (CPA), the acute cessation of blood flow and ventilation, is fatal if left untreated. Cardiopulmonary resuscitation (CPR) is targeted at restoring oxygen delivery to tissues to mitigate ischemic injury and to provide energy substrate to the tissues in order to achieve return of spontaneous circulation (ROSC). In addition to basic life support (BLS), targeted at replacing the mechanical aspects of circulation and ventilation, adjunctive advanced life support (ALS) interventions, such as intravenous fluid therapy, can improve the likelihood of ROSC depending on the specific characteristics of the patient. In hypovolemic patients with CPA, intravenous fluid boluses to improve preload and cardiac output are likely beneficial, and the use of hypertonic saline may confer additional neuroprotective effects. However, in euvolemic patients, isotonic or hypertonic crystalloid boluses may be detrimental due to decreased tissue blood flow caused by compromised tissue perfusion pressures. Synthetic colloids have not been shown to be beneficial in patients in CPA, and given their documented potential for harm, they are not recommended. Patients with documented electrolyte abnormalities such as hypokalemia or hyperkalemia benefit from therapy targeted at those disturbances, and patients with CPA induced by lipid soluble toxins may benefit from intravenous lipid emulsion therapy. Patients with prolonged CPA that have developed significant acidemia may benefit from intravenous buffer therapy, but patients with acute CPA may be harmed by buffers. In general, ALS fluid therapies should be used only if specific indications are present in the individual patient.

Keywords: cardiopulmonary resuscitation, fluid resusciation, bicarbonate, lipid emulsion infusion, dogs, cats, calcium gluconate

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INTRODUCTION

Untreated cardiopulmonary arrest (CPA), the acute cessation of blood flow and ventilation, is uniformly fatal, and the only known treatment to reverse it is cardiopulmonary resuscitation (CPR). CPR is delivered in two phases. The first and most important phase, basic life support (BLS), consists of chest compressions to re-establish blood flow and oxygen delivery to the tissues, and ventilation, to oxygenate the arterial blood and excrete carbon dioxide. The second phase of CPR, advanced life support (ALS), consists of adjunctive therapies that are targeted at improving the efficacy of the BLS interventions to maximize oxygen delivery to the tissues through drug therapy and defibrillation.

Intravenous fluid bolus therapy has been commonly used to increase preload during CPR in an attempt to increase cardiac output. In addition, specific fluid therapies to address acid-base and electrolyte disturbances that occur commonly in patients with CPA have been proposed. Finally,

the use of intravenous lipid emulsions for the treatment of CPA secondary to specific toxicities has been studied. In 2012, the Reassessment Campaign on Veterinary Resuscitation (RECOVER) Initiative published the first evidence-based veterinary CPR guidelines after an extensive review of the primary literature (1). This manuscript summarizes the current evidence for and against the use of intravenous fluids, blood products, treatment of electrolyte disturbances, lipid emulsion and buffer therapy during CPR as well as the evidence-based RECOVER clinical guidelines related to these therapies.

RESUSCITATIVE FLUID THERAPY DURING CPR

The Effect of Fluid Loading During CPR

The primary goal of CPR is to restore oxygen delivery to tissues. Oxygen delivery is the product of cardiac output and arterial oxygen content, as shown in **Figure 1**. Basic life support targets both aspects of oxygen delivery by generating cardiac output through chest compressions and increasing arterial hemoglobin saturation through positive pressure ventilation. Once BLS is initiated, ALS interventions are targeted at enhancing oxygen delivery through various supplemental drug and defibrillation therapies, including intravenous fluid therapy.

As demonstrated in **Figure 1**, cardiac output is the product of stroke volume and heart rate. One of the three determinants of stroke volume is preload, defined as end-diastolic ventricular wall tension or wall stretch, and clinically often represented as left ventricular end-diastolic volume or pressure (2). Preload can be increased in several ways, including through the infusion of intravenous fluids. However, the relationship between preload and stroke volume is not linear and is described by the Frank-Starling curve (**Figure 2**) (3). This shows that increasing a low preload leads to progressively increased stroke volume. This is because increased preload leads to left ventricular stretch, causing an increased contraction of the ventricle and improved stroke volume. After preload reaches and optimal volume, substantial further increases cause a diminished stroke volume, although this may largely be due to diastolic ventricular interaction rather than an overstretch of myocardial sarcomers (4).

Tissue perfusion is dependent on adequate cardiac output, but microvascular blood flow, and hence oxygen delivery to tissues is ultimately dependent on tissue perfusion pressures, which determine the amount of blood flow at the level of the tissue bed. The primary goal of CPR is to maintain perfusion of the core organs, the heart and the brain. In order to restore spontaneous circulation, restoration of blood flow and oxygen delivery to the myocardium is critical. Until adequate myocardial energy substrates are established, return of spontaneous circulation (ROSC) is unlikely. The coronary arteries arise from the base of the aorta just as it leaves the left ventricle and supply oxygen to the myocardium. Large epicardial vessels branch into smaller intramuscular vessels and ultimately to the myocardium before entering the capillary beds where

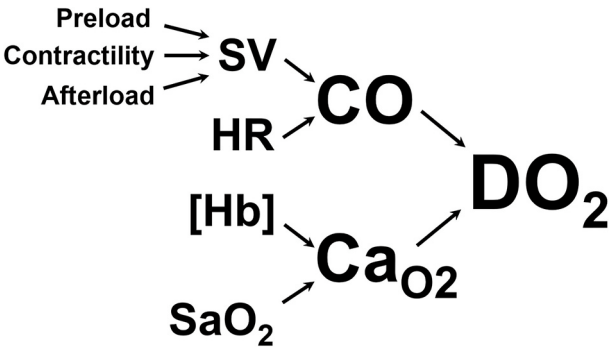

FIGURE 1 | Oxygen delivery to the tissues (DO_2) is the product of cardiac output (CO, the volume of blood ejected from the left ventricle into the aorta per minute) and arterial oxygen content (Ca_{O2}, the volume of oxygen carried in the arterial blood). CO is the product of heart rate (HR) and stroke volume (SV, the volume of blood ejected from the left ventricle with each contraction). SV is determined by preload (the amount of blood in the left ventricle at the end of diastole), contractility (the force with which the left ventricle contracts), and afterload (the pressure against which the left ventricle has to push to get blood into the aorta). Ca_{O2} is determined by the amount of hemoglobin per unit of volume of blood ([Hb]) and the amount of that hemoglobin that is saturated with oxygen in the arterial blood (S_aO_2).

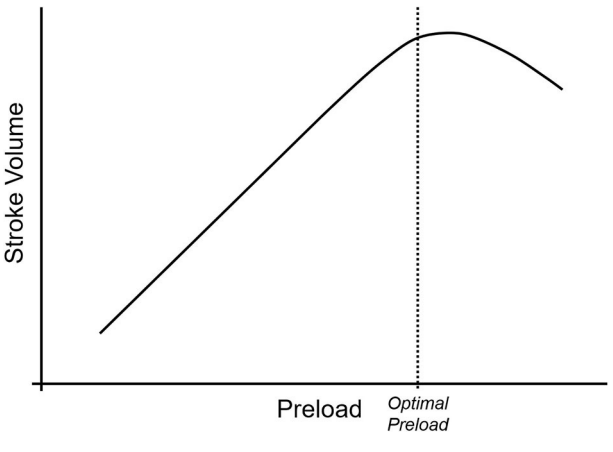

FIGURE 2 | The Frank-Starling curve describes the relationship between preload (on the x-axis) and stroke volume (on the y-axis). At low preload, increases in the preload lead to linear increases in stroke volume due to increasing ventricular stretch. As the myocytes reach their maximum stretch capacity, the rate of stroke volume increase begins to drop with increasing preload, and as the myocytes become over-stretched, stroke volume begins to drop with increasing preload.

Abbreviations: ADP, aortic diastolic pressure; ALS, advanced life support; BLS, basic life support; CCB, calcium channel blocker; CePP, cerebral perfusion pressure; CoPP, coronary perfusion pressure; CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; ETCO2, end tidal CO2; HES, hydroxyethyl starch; HHS, hypertonic saline/hydroxyethyl starch combination; HS, hypertonic saline 7.2%; IHCA, in-hospital cardiac arrest; ICP, intracranial pressure; LAST, local anesthetic systemic toxicity; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; MAP, mean arterial pressure; NaBic, sodium bicarbonate; OHCA, out-of-hospital cardiac arrest; RECOVER, Reassessment Campaign on Veterinary Resuscitation; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; SD, standard deviation; VF, ventricular fibrillation.

oxygen delivery occurs. Venous drainage from the capillary beds feed into myocardial and then epicardial coronary veins. The latter ultimately coalesce into the coronary sinus, which drains into the right atrium. During systole, the myocardium contracts and compresses the myocardial coronary arteries, dramatically increasing resistance. Therefore, in the spontaneously beating heart, the bulk of myocardial perfusion occurs during ventricular diastole when the myocardium relaxes and myocardial coronary arterial resistance decreases. The driving pressure for blood flow into the myocardium during diastole is the aortic diastolic pressure (ADP). However, this driving pressure is resisted by the pressure within the left ventricle at the end of diastole (LVEDP) since the myocardial coronary arteries serving the left ventricle are exposed to left ventricular pressures as they course into the endocardium. During CPR, left ventricular end-diastolic pressures (i.e., the ventricular pressure during the relaxation phase of chest compressions) are very low, commonly less than the right atrial pressure (RAP), and coronary arterioles are maximally vasodilated (5). Therefore, the net force driving myocardial perfusion during CPR, termed coronary perfusion pressure (CoPP), is the difference between the driving pressure (aortic diastolic pressure) and the outflow pressure (right atrial diastolic pressure, RADP).

$$\text{CoPP} = \text{ADP} - \text{RADP}$$

Figure 3 shows aortic and right atrial pressure waveforms from a pig undergoing mechanical chest compressions. In this figure, the CoPP is calculated at the end of diastole, but other methods are used and this must be taken into consideration when comparing CoPP values across publications (6). Adequate CoPP has been shown to be critical for successful resuscitation from CPA in dogs. In early experimental studies using asphyxial CPA in dogs, it appeared that the CoPP required for ROSC was 30–40 mm Hg. This could not be achieved with chest compressions alone but required the addition of epinephrine (7). Further experimental studies in dogs conducted by Kern and colleagues in the 1980s demonstrated that a CoPP of at least 20 mm Hg led to ROSC, but 30 mm Hg was required for survival of more than 24 h (8). In an observational study in people including 100 adults with normothermic, non-traumatic CPA, non-survivors had a mean maximum CoPP of 8.4 mm Hg (SD 10 mm Hg), while those with ROSC achieved a mean maximum CoPP of 25.6 mm Hg (SD 7.7 mm Hg) (9).

Similarly, the pressure gradient leading to cerebral blood flow is cerebral perfusion pressure (CePP). The primary driving pressure for cerebral blood flow is mean arterial pressure (MAP), and the counteracting outflow pressure is either central venous pressure (CVP) or intracranial pressure (ICP), whichever is greater (CePP = MAP-CVP or MAP-ICP).

The dependence of tissue blood flow on perfusion pressures has a substantial impact on fluid therapy during CPR. Intravenous fluid loading has the potential to increase tissue driving pressures by increasing ADP and MAP during CPR. However, such fluid loading may also increase the counteracting outflow pressures, both RADP and CVP, which will decrease CoPP and CePP, respectively, and worsen oxygen delivery to myocardial and cerebral tissue beds. Ultimately, intravenous fluid loading should only be administered during CPR if it is likely that an increase in driving pressure (ADP or MAP) rather than in outflow pressure (RADP and CVP) will occur. By definition, this is more likely in patients that are effectively hypovolemic, either due to intravascular volume losses or inappropriate vasodilation (e.g., sepsis, SIRS, anaphylaxis). However, patients that are already fully fluid loaded or euvolemic will not likely experience significant increases in driving pressure. Rather, a further rise in intravascular volume in these patients will predominantly increase the outflow pressure (RADP and CVP), which will decrease perfusion pressures and result in decreased blood flow to the tissues.

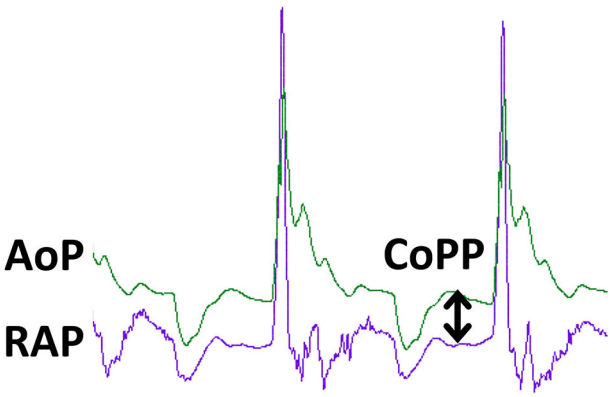

FIGURE 3 | Pressure tracings during CPR in an experimental swine ventricular fibrillation model. The green tracing is aortic pressure (AoP) and the purple tracing is right atrial pressure (RAP). The peaks correspond to the compression phase of CPR. Coronary blood flow and oxygen delivery occur during the relaxation phase of chest compressions and is proportional to coronary perfusion pressure (CoPP), the difference between aortic pressure and right atrial pressure at the end of the relaxation phase, as denoted by the double arrowed vertical line. The tracing was obtained during mechanical, sternal chest compressions (100/min) delivered by the LUCAS (Lund University Cardiopulmonary Assist System) device to an anesthetized pig with VF arrest. Solid state pressure transducer catheters (Micro-Tip® Transducer, Millar Instruments, Houston, TX) were introduced through the left femoral artery and vein for continuous measurement of AoP and RAP.

These theoretical concerns have been documented in experimental studies. In a study of 18 euvolemic dogs with induced CPA, infusion of 11 ml/kg of either lactated Ringer's solution or whole blood resulted in a 34% increase in cardiac output, but a concurrent 26% decrease in left ventricular blood flow and a 35% decrease in cerebral blood flow. This was explained by a 22% reduction in CoPP that resulted from a disproportional increase in RADP compared to ADP (10). Similarly, Ditchey and Lindenfeld (11) found that volume loading during CPR in euvolemic dogs decreased cerebral and coronary blood flow due to increases in RADP and ICP that surpassed the increases in aortic systolic and diastolic pressures. In another study in euvolemic dogs with induced CPA, administration of intravenous fluid boluses in addition to epinephrine resulted in significant increases in aortic systolic and diastolic pressures and right atrial pressure, but no significant increase in myocardial

blood flow compared to administration of epinephrine alone, suggesting that CoPP was not improved with fluid boluses in dogs receiving epinephrine (12). In euvolemic swine, the bolus administration of ∼30 mL/kg of 0.9% saline reduced CoPP from 20.6 ± 8 mm Hg to 12.8 ± 5 mm Hg and significantly compromised ROSC (13). Unfortunately, to date there are no controlled, large-scale clinical trials evaluating the use of intravenous fluid boluses in euvolemic patients.

In patients with acute CPA, assessment of intravascular volume status can be challenging. Typical physical examination parameters that may be helpful, such as capillary refill time, mucous membrane color, heart rate and pulse quality, cannot be assessed in patients with CPA. Therefore, review of pre-arrest physical exam findings, an understanding of the precipitating causes of the arrest (e.g., a history of substantial gastrointestinal or urinary fluid losses or of anaphylaxis), or evidence of acute blood loss (e.g., documented external, cavity, or GI bleeding) are required to make the best intravenous fluid therapy plan during CPR. The RECOVER ALS guidelines recommend a conservative approach to fluid administration during CPR, reserving fluid boluses only for patients with known or suspected hypovolemia or distributive shock (1).

Types of Resuscitation Fluids

As described previously, for hypovolemic patients in CPA, fluid boluses are recommended because they are likely to increase tissue driving pressures more than outflow pressures and improve CoPP and CePP. Generally, isotonic crystalloid fluid boluses of 1/4–1/3 of the total blood volume over 15–20 min (20–30 ml/kg in dogs, 10–20 ml/kg in cats) are recommended to treat hypovolemia.

There is experimental evidence that hypertonic saline (HS) may have beneficial effects beyond volume expansion during CPR. It is posited that HS may have neuroprotective effects by reducing cerebral edema, neuronal excitotoxicity, inflammation, and neuronal apoptosis. A recent experimental study in rats showed improved neurologic outcome post-CPR and reduced hippocampal apoptosis in rats receiving hypertonic saline during CPR compared to rats receiving isotonic crystalloids or synthetic colloids (14). Importantly, the study design did not include a control group that underwent CPR without fluid administration. An experimental study in cats in which CPR was started after 15 min of untreated VF, the investigators examined the effect of HS/hydroxyethyl starch (HES) (2 mL/kg IV) administered early during CPR compared to standard resuscitation without any fluid administration. The HS/HES combination resulted in a decreased CoPP and CePP during CPR compared to controls, but cats in the experimental group had significantly smaller volumes of frontal cortex no-reflow regions (areas of the brain in which there was no evidence of microvascular blood flow) 30 min after ROSC (15). A more recent study in swine compared administration of HS, HES, the combination of HS/HES (HHS), or normal saline (2 mL/kg IV once over 10 min) during open-chest CPR and showed that pigs in the HS and HHS group had increased myocardial blood flow and ROSC rates despite similar CoPP to the other 2 groups (16). Of note, a control group that received no fluids during CPR was lacking. Taken together, these studies suggest a potential neurologic benefit to administration of HS due to improved cerebral microcirculation and myocardial blood flow during CPR despite a possible decrease in CoPP and CePP, but the long-term outcome effects are unknown at this time.

There is limited clinical data available to inform a decision about the use of HS during CPR. A prospective, randomized controlled clinical trial (RCT) of 200 human patients with out-of-hospital cardiac arrest (OHCA) in which 100 patients received 2 ml/kg of HHS and 100 patients received 2 ml/kg of HES over 10 min showed no difference in short or long-term outcomes between the groups (17). A retrospective, registry-based study from Germany comparing human patients with OHCA who received either a HHS bolus at 2 ml/kg compared to a matched control group that received standard care without HHS showed improved survival to hospital admission with ROSC in the HHS group (18). However, long-term outcomes and survival to hospital discharge were not evaluated in this study. In addition, an accompanying editorial noted that short-term survival does not necessarily correlate with long-term survival or good functional outcome, that there are serious concerns about the safety of HES, and that there was no control for CPR quality in this retrospective study. These concerns suggest that more research is needed before this type of fluid resuscitation can be recommended routinely during CPR (19).

Taken together, this evidence suggests that HS may have a benefit over isotonic crystalloid fluids during CPR in patients with hypovolemia or vasodilatory shock. Given the consistent finding that intravenous fluid boluses of any kind lead to decreases in CoPP and CePP, and in the absence of any long-term outcome studies demonstrating a survival or neurologic function benefit to the use of HS during CPR in euvolemic patients, it is difficult to recommend volume expansion of any kind in patients known or suspected to be euvolemic during CPR. Taken in context with recent evidence of harm associated with the administration of HES (20) and the lack of any clinical or experimental evidence of benefit during or after CPR, the use of synthetic colloids alone or in combination with HS during CPR cannot be recommended.

Where CPA is caused or compounded by hypovolemia, fluid resuscitation is recommended as outlined above, and where hypovolemia is the consequence of severe hemorrhage, those fluids should include blood products (21). While there is very limited specific evidence to guide management of CPA due to exsanguination, it is reasonable to manage these cases similarly to patients with hemorrhagic shock not in CPA. A recent porcine study in which exsanguination cardiac arrest was induced by peripheral arterial hemorrhage, intra-arrest resuscitation with whole blood compared to 0.9% NaCl was significantly more effective in achieving ROSC (22). In people, a combination of fresh frozen plasma (FFP) and packed red blood cells (PRBC) at a ratio of 1:1 or 1:2 has been suggested, with the addition of cryoprecipitate and platelet concentrate as needed to prevent dilution of fibrinogen and platelets (23). In an RCT in people with hemorrhage after severe trauma, a lower relative amount of PRBC (FFP:PLT:PRBC = 1:1:1) compared to more PRBC (1:1:2)

led to improved hemostasis, as more FFP and platelets were administered, and decreased death due to exsanguination but not overall mortality (24). Blood products can be administered by the intraosseus route (IO) initially until venous catheterization can be established. Studies in swine showed that administration of whole blood with a pressure bag inflated to 300 mm Hg will not lead to more hemolysis when blood is given by the IO route compared to a peripheral intravenous catheter, but that the infusion rate may be slower for IO (i.e., 40–100% of IV rate, depending on IO location) (25, 26).

Successful resuscitation from traumatic CPA is resource intensive. In addition to massive transfusion therapy, effective management of severe traumatic hemorrhage requires a comprehensive strategy potentially including damage control surgery, minimization of crystalloid administration, treatment of hyperfibrinolysis (e.g., tranexamic acid or aminocaproic acid), permissive hypotension and other interventions (27, 28). In people, many correctable causes for traumatic cardiac arrest require thoracotomy or thoracostomy (28). There are no studies published that specifically examine the use of blood transfusion during veterinary CPR or the causes, treatment and outcomes of traumatic CPA in dogs or cats. One veterinary case report describes the intra-arrest xenotransfusion of canine blood to a cat with severe anemia that ultimately survived to hospital discharge, an example for the potential benefit of intra-arrest red blood cell transfusions for reasons other than severe hemorrhage (29).

Administration of Ice-Cold Fluids for Intra-Arrest or Early Post-Cardiac Arrest Cooling

Hypothermia protects all tissues, but in particular the brain, from the consequences of ischemia and reperfusion by a multitude of mechanisms (30). The post-cardiac arrest maintenance of body temperature below normal (i.e., targeted temperature management [TTM]) is currently recommended in humans that remain comatose with ROSC after out-of-hospital or in-hospital cardiac arrest (31). The 2012 RECOVER guidelines recommend that in dogs or cats that remain comatose after CPA, hypothermia to a core temperature of 32–34°C should be instituted as quickly as possible and maintained for 24–48 h (1). When considering all experimental animals studies involving rodents, swine, cats and dogs, hypothermia during the arrest has the most profound and long-lasting effect and any delay in hypothermia reduces the benefit (32–36). Thus, cooling that occurs during CPR and before ROSC might show benefit over post-cardiac arrest cooling alone. Animal experimental and human clinical studies evaluating intra-arrest therapeutic hypothermia explored selective brain cooling techniques (e.g., ice caps, nasopharyngeal cooling, or carotid flush) or systemic cooling approaches such as surface cooling with blankets, intravascular cooling catheters and intravenous administration of ice-cold fluids (34).

Experimental studies using intra-arrest cooling by ice-cold fluid bolus infusion are limited to swine (37, 38). In an OHCA model where ventricular fibrillation (VF) was left untreated for 8 min followed by CPR for at least 5 min before first defibrillation, more animals with intra-arrest cooling achieved ROSC (12/14) compared to those that were not cooled (6/14). The cooling group received a rapid intravenous bolus of 30 mL/kg of normal saline at 4°C during ongoing chest compressions, while the normothermic group received the same volume of saline at body temperature (37 ± 1°C). In these swine with a body weight of 27 ± 2.3 kg, the cold saline was effective in reducing the core body temperature to 34.2 ± 2.3°C within 5 min (37). In a second study, using a comparable VF model in similarly sized pigs, 30 mL/kg of acetated Ringer's solution at 4°C or at room temperature was infused over 22 min, starting early during CPR. With this slower administration regimen, the maximum temperature decrease achieved was only 1.62 ± 0.23°C in the cooling group compared to 1.14 ± 0.23°C in the control group, and the cold intra-arrest fluid conveyed no benefit on ROSC or survival to 3 h (38). These studies did not report any harm subsequent to fluid loading, but relevant assessments such as for presence or absence of pulmonary edema were not provided, and notably, control groups received the same amount of fluids. A further study in swine with VF subsequent to coronary occlusion demonstrated that the fluid loading with both ice-cold and room temperature saline during CPR (30 mL/kg) reduced CoPP by 40% when compared to no fluid administration (13). Thus, while the preponderance of animal studies supports intra-arrest cooling by a multitude of techniques and especially with prolonged CPA, evidence suggests that intra-arrest administration of large volumes of ice-cold saline is not beneficial in normovolemic animals (34). This could indicate that the benefits of cooling are offset by the harm of intra-arrest fluid loading.

A single randomized controlled trial in humans including 245 subjects with OHCA of any rhythm studied the effect of intra-arrest cooling with intravenous cold saline compared to no such cooling (39). Up to 2 L of ice-cold 0.9% saline were administered with a pressure bag, in combination with surface cooling with gel pads. It effectively reduced the core temperature and shortened the time to reach target temperature (34°C) by 75 min. However, intra-arrest cooling did not affect patient clinical outcome or surrogate markers of neurological injury. Likewise, a more recent non-RCT trial did not find any association between intra-arrest cooling of OHCA patients and important outcome measures such as sustained ROSC and survival to discharge (40).

Animal research suggests that early induction of hypothermia after ROSC is superior to delayed cooling (32). Intravenous administration of ice-cold isotonic saline represents an easy, rapid and cheap method to achieve this goal, and allows pre-hospital application in people. In swine, infusion of 4°C cold 0.9% saline at 30 mL/kg immediately after ROSC led to significantly improved short term neurological outcome compared to saline administration at room temperature (41). This cooling technique has otherwise not been specifically studied in animals but has been widely tested in people for almost 20 years. To date, six RCTs including a total of 2,500 subjects, did not show any benefit of early post-cardiac arrest cooling with rapid cold isotonic crystalloid infusion (42). Similar to the intra-arrest studies, boluses of up to 2 L of 0.9% saline, lactated Ringer's solution or Ringer's acetate at a rate of 100 mL/min were administered. Core temperature was ∼1°C less than controls at hospital admission, but none of the studies showed improved favorable neurological

outcome or survival to discharge. The largest study including 1,359 subjects demonstrated a significantly higher risk of re-arrest and occurrence of pulmonary edema in the pre-hospital cooling group (43). Thus, the routine administration of pre-hospital cooling with cold fluids is currently not recommended in people (31).

In summary, available evidence from animal studies suggest that mild hypothermia itself, either applied intra-arrest or early after ROSC mitigates ischemia-reperfusion injury. However, the harm associated with administration of large intravenous boluses of cold isotonic crystalloids during or after CPR suggests that other avenues for cooling should be considered in most cases. As dogs and cats are generally of lower thermal mass than humans, hypothermia (e.g., core temperature of 36°C or less) often occurs spontaneously during treatment of CPA and rapid administration of cold fluids is likely not necessary.

NON-RESUSCITATIVE FLUID THERAPY DURING CPR

Electrolyte Administration

Under special circumstances, the intra-arrest administration of calcium, magnesium, potassium and dextrose can be considered, but evidence of broad benefit is lacking.

Hyperkalemia can occur for a multitude of reasons and can lead to life-threatening cardiotoxicity and cardiopulmonary arrest once serum potassium concentrations are severely increased (e.g., >6.5 mEq/L) (44). Intravenous calcium administration should be considered when CPA is caused by hyperkalemia, in combination with other measures described for management of hyperkalemia-related cardiotoxicity and standard ALS interventions. Specifically, this includes infusion of 10% calcium gluconate (0.5–1 mL/kg, IV or IO) over 2–5 min, sodium bicarbonate (NaBic, 1 mEq/kg IV) over 2–5 min, and a mixture of regular insulin (0.5 U/kg) with 50% dextrose (2 g/kg) over 5 min intravenously (21). Calcium gluconate (0.5–1 mL/kg, IV or IO over 2–5 min) should further be given if CPA is attributed to hypocalcemia or to calcium channel blocker (CCB) overdose. For the latter, it has been recommended in people that calcium administration should be combined with lipid emulsion therapy (see below) (45). High dose insulin (e.g., bolus 0.5–2 U/kg followed by 0.5–2 U/kg/h infusion) together with dextrose in order to prevent hypoglycemia (e.g., 10–20% dextrose infusion) was also found to be effective in human case series of severe CCB poisoning and could be considered in people and animals (46–48). There is no indication in the literature that routine administration of calcium during CPR is beneficial, and hypercalcemia during reperfusion could be injurious by worsening post-ischemic cytoplasmatic calcium overload, although such evidence is experimental only (49–51). The 2012 RECOVER guidelines advise against routine administration of calcium during CPR but indicates that it may be considered in the presence of moderate to severe hypocalcemia (1).

As for calcium, there is no conclusive evidence for an overall benefit of routine administration of magnesium during cardiac arrest, despite several RCTs in people examining the utility of magnesium in OHCA and IHCA (52). Nevertheless, magnesium administration may be considered with some forms of pulseless ventricular tachycardia (pVT) (i.e., torsades de pointes), and possibly with pVT in general, or where it occurs in the presence of hypomagnesemia (46). In such situations, IV magnesium sulfate (15–25 mg/kg IV, bolus push) is recommended in humans, and similar doses have been suggested for dogs (12–40 mg/kg IV, slow bolus) (21, 53, 54).

Experimentally induced hypokalemia in dogs below 3.0 mEq/L was found to increase vulnerability to ventricular tachycardia and fibrillation through a variety of arrhythmia mechanisms (55–57). While expedient correction of the hypokalemia is reasonable, bolus administration of potassium during CPA is untested and not recommended (21). Instead, a potassium chloride CRI at 0.5 mEq/kg/hr should be considered.

Intravenous Lipid Emulsions

The use of intravenous lipid emulsions (ILE) has been extensively reported in veterinary medicine to treat a wide range of poisonings and has recently been reviewed (58). In the context of CPA, it has been studied most extensively to reverse the effects of local anesthetic systemic toxicity (LAST), and a recent meta-analysis found ILE to improve survival in animal models including rats, rabbits, swine and dogs (59). In an experimental canine study, cardiac arrest was induced by rapid administration of bupivacaine (10 mg/kg) to isoflurane-anesthetized dogs. After 10 min of open-chest CPR, a 4 mL/kg bolus of a 20% lipid emulsion or 0.9% saline was followed by an infusion at 0.5 mL/kg/min for 10 min. All ILE treated dogs (6/6) and none of the saline treated dogs survived (60). There are many potential mechanisms of ILE's beneficial effects (61). The most popular theory is that ILE acts as a lipid sink and thus removes lipid soluble compounds from the target tissue, attenuating their toxic effect. In addition, there is some evidence that ILE elicits an additional cardiotonic response that is not explained by local anesthetic sequestration alone (62). Furthermore, studies in rats suggest that ILE may lessen ischemia-reperfusion injury by mitigating mitochondrial permeability transition (63, 64). Despite the lack of human RCTs or any clinical studies in veterinary species, the preponderance of the evidence suggests that ILE should be administered in dogs and cats with CPA caused by LAST.

The general recommendation for the clinical use of ILE in dogs and cats is (a) to administer 20% formulations, as 10% solutions are less effective; (b) to use inline filters (1.2 micron) as lipid aggregates are common; (c) to administer the solution as a bolus (1.5 mL/kg IV over 1 min) followed by an infusion (0.25 mL/kg/min IV CRI) for 30–60 min; (d) to limit the daily dose to 10 mL/kg (58). To facilitate administration during CPR, it appears reasonable to use repeat boluses of 1.5 mL/kg every second BLS cycle (i.e., every 4 min) instead of a

constant rate infusion. Even though ILE might interfere with the hemodynamic response to epinephrine, it is currently not recommended in humans to adjust standard ALS measures (65).

Poisoning with other drugs than local anesthetics may also warrant the administration of ILE during CPR. Treatment with ILE is recommended in humans, and in extension animals, with CCB overdose alongside calcium gluconate, ALS measures as per standard guidelines and possibly other measures such as insulin/dextrose (45, 47). Two case reports including dogs with severe cardiotoxicity subsequent to CBB ingestion (i.e., diltiazem and lamotrigine) document successful use of ILE (48, 66). Unlike for CCB, the evidence for the benefit of ILE for the treatment of beta-blocker poisoning is conflicting (67). Human data consist of 1 observational study, 10 case series and 21 case reports, but inconsistent outcomes and co-administration of several other interventions disallow assessment for any benefit. The reports in people are complemented by 5 experimental studies in rabbits, none of which showed a significant treatment effect in support of ILE (67). The prospect of ILE as an effective antidote to other lipophilic compounds relevant to CPA, such as tricyclic antidepressants, may be considered on a case by case basis, following a similar ILE intra-arrest administration regimen as outlined for CCB above.

Adverse effects of ILE therapy, while infrequent, deserve mention (58). In a rabbit model of asphyxia CPA, ROSC rates with intralipid (3 mL/kg) compared to saline were significantly reduced (68). In one case report, a dog developed an acute respiratory distress-like syndrome after standard dose ILE administration (69). A systematic review further identified a long list of possible adverse effects in 27 animal and 87 human studies, including acute kidney injury, ventilation perfusion mismatch, acute lung injury, pancreatitis, hypersensitivity reactions, increased infection susceptibility, and CPA (70). In addition, the hyperlipidemia resulting from ILE therapy will compromise laboratory testing.

Buffer Therapy

Clinical CPA causes profound acid-base abnormalities in dogs and cats, characterized by extreme venous acidemia with a pH as low as 6.6, venous hypercarbia that can reach beyond 100 mm Hg and a pronounced base deficit of more than 20 mmol/L, that continue into the early reperfusion phase (71). An experimental study in swine demonstrated that after 3 min of untreated VF arrest and 8 min of CPR, the intramyocardial pH decreased to <6.5 and the intramyocardial PCO_2 rose above 350 mm Hg (72). As for all endogenous cases of severe acidosis, resolution and thus survival ultimately depends on reversal of the cause. In the context of CPA, resolution of acidosis requires reinstitution of adequate tissue blood flow through ROSC. However, severe acidosis alone may lead to changes in cellular metabolism that hinders reinstitution of critical myocardial function, although the relationship between pH and cellular dysfunction varies with animal species, temperature and severity and type of acidosis (73). Experimental studies have shown that low tissue pH can have profound effects on cellular function, such as reduced myocardial contractility and loss of myocardial beta-adrenoreceptor responsiveness (74–76). Based on the assumption that the extreme cellular acidosis occurring during CPA is harmful, intra-arrest buffer therapy has been widely studied in experimental animal and human studies.

Several experimental studies in dogs found a benefit of buffer administration during CPR. Sanders et al. (77) in a prolonged VF model of CPA using dogs (20–30 kg bodyweight) administered 25 mEq of NaBic prior to induction of VF, 20 mEq NaBic after 5 min of VF, 10 mEq every 5 min thereafter and 50 mEq after the first defibrillation attempt. No vasopressors or other drugs were administered, and defibrillation was attempted after 30 min of chest compressions. Bicarbonate administration improved both ROSC and survival to 24 h. Vukmir and colleague demonstrated that the benefit of NaBic varies with the duration of untreated CPA. In dogs experiencing untreated VF CPA for either 5 or 15 min, 1 mEq/kg of NaBic and subsequent additional boluses to maintain the base excess above -5 mmol/L were administered in addition to standard ALS. Buffer therapy markedly improved ROSC rates after prolonged CPA (15 min CPR) compared to ALS without NaBic but showed no benefit with short CPA (5 min CPR). In addition, CoPP in the NaBic group (35.6 ± 25.2 mm Hg) was found to be more than double that in the control group (15.3 ± 16.0 mm Hg) in the dogs with prolonged CPA (78). In a third study, NaBic administration (2 mEq/kg, once) at the beginning of CPR after 10 min of untreated VF improved ROSC and short term survival, reduced the number of required defibrillation attempts, and increased CoPP (23 ± 6 vs. 9 ± 2 mm Hg) compared to 0.9% saline in control animals (79). In a similar canine CPA model, NaBic (1 mEq/kg, once) or an equivalent dose of alternative buffer administered after 18 min of CPA (10 min of untreated VF and 8 min of CPR), improved ROSC and shortened the duration to successful defibrillation (80). But not all canine studies are supportive of buffer administration. Two additional experimental canine studies with overall shorter durations of untreated VF or CPR showed no benefit of intra-arrest buffer therapy (81, 82). A series of canine studies conducted by Bleske and colleagues did not find any benefit of buffer therapy but established that alkalemia can result from indiscriminate administration of NaBic. The CPA model used in these studies was less injurious than those presented above and animals suffered from only moderate levels of acidemia (83–85). An additional canine study demonstrated that a very large dose of NaBic (0.43 mEq/kg/min of arrest) will reliably lead to profound arterial alkalemia and hypercapnia, and a paradoxical decrease in CSF pH (see paragraph below) (86). In addition, two swine CPR studies with shorter durations of ischemic/anoxic insults failed to reveal any benefit of buffer administration (87, 88). Taken together, these experimental canine studies suggest that buffer therapy might be beneficial if applied after prolonged cardiac arrest, and thus in the presence of severe acidosis, and when used in conjunction with standard ALS treatment including vasopressors.

A major theoretical concern with NaBic-treatment of acidosis is that CO_2 is generated as bicarbonate buffers protons. This increase in CO_2 is reflected in a rise in $PaCO_2$ and $EtCO_2$ of

5–10 mm Hg for 1–3 min that can be observed after intra-arrest administration of NaBic (1–2 mEq/kg) (83, 87, 89). In contrast to bicarbonate, CO_2 is capable of rapidly entering the intracellular space thereby "paradoxically" worsening cytosolic acidosis and potentially further disrupting cell function. However, this *in vitro* effect is of questionable relevance *in vivo* (90). Non-CO_2 generating buffers, such as CarbiCarb (an equimolar solution of Na_2CO_3 and $NaHCO_3$) or THAM (tromethamine, an organic amine buffer) were tested as alternatives to bicarbonate, but studies in dogs and swine did not show any benefit over NaBic (80, 87, 88). Moreover, NaBic was at least as effective in correcting cerebral pH in dogs after cardiac arrest as THAM and paradoxical cerebral acidosis was not observed with either of the compounds (91). In fact, animal studies suggest a neuroprotective effect of buffer therapy during cardiac arrest with improved cerebral perfusion, attenuated cerebral acidosis, and reduced cerebral glutamate and neuronal ischemic cell death (92, 93). Moreover, the non-CO_2 generating buffer CarbiCarb did not improve myocardial tissue pH in swine during CPR when compared to NaBic (88).

In people, 2 RCTs and one systematic review that incorporates the findings of observational studies with a total of more than 18,000 patients showed no overall benefit of intra-arrest buffer therapy, with some studies reporting worse outcomes with buffer therapy (94–96). One RCT showed a significant benefit of NaBic administration (1 mEq/kg) in the subpopulation experiencing ALS of more than 15 min (95).

The last evidence evaluation by the International Liaison Committee on Resuscitation examining intra-arrest buffer therapy was conducted in 2010 and did not recommend routine administration of NaBic or any other buffer (46). However, the 2010 AHA guidelines recommend that in special circumstances such as hyperkalemia, severe preexisting acidemia or certain poisonings administration of NaBic (1 mEq/kg IV) can be considered, while care must be taken to avoid potential adverse effects such as hypernatremia or iatrogenic alkalemia (97). For dogs and cats, the 2012 RECOVER guidelines recommend that NaBic administration (1 mEq/kg IV) may be considered in addition to standard ALS in animals when CPA continues for more than 10–15 min (1).

AUTHOR CONTRIBUTIONS

DF and MB co-wrote and critically revised the manuscript. Both authors read and approved the final manuscript.

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Fluid Overload

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Fluid overload (FO) is characterized by hypervolemia, edema, or both. In clinical practice it is usually suspected when a patient shows evidence of pulmonary edema, peripheral edema, or body cavity effusion. FO may be a consequence of spontaneous disease, or may be a complication of intravenous fluid therapy. Most clinical studies of the association of FO with fluid therapy and risk of harm define it in terms of an increase in body weight of at least 5–10%, or a positive fluid balance of the same magnitude when fluid intake and urine output are measured. Numerous observational clinical studies in humans have demonstrated an association between FO, adverse events, and mortality, as have two retrospective observational studies in dogs and cats. The risk of FO may be minimized by limiting resuscitation fluid to the smallest amount needed to optimize cardiac output and then limiting maintenance fluid to the amount needed to replace ongoing normal and pathological losses of water and sodium.

Keywords: fluid overload, hypervolemia, edema, effusion, fluid balance, resuscitation, stabilization

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The mammalian stress response to injury, hypovolemia, or critical illness includes retention of sodium and water and, at least early on, increased thirst (1–5). These responses may serve to defend blood volume and maintain hydration when access to water is impaired by debility, and in the absence of medical care likely confer some survival advantage. However, the application of modern intensive care sets the stage for harm when potentially limitless amounts water and sodium can be administered to patients whose upset biology favors retention of both. Although evolutionary pressure likely selected for the adaptive responses to hypovolemia following injury or illness, there was no such selection pressure to respond to hypervolemia in the same setting, a situation now commonly referred to as fluid overload (FO).

The concept of FO as a clinical entity to be avoided appeared in earnest within the medical literature during the 1970's, with 54 PubMed citations from that decade using that phrase. Although for many years FO has been recognized as a potential complication of anuria in chronic hemodialysis patients, in this century the phrase has more often been used to describe a complication of fluid therapy in any patient at risk for hypervolemia or edema. The importance of FO has been underlined by a growing number of reports of observational studies that associate the condition with higher morbidity and mortality in hospitalized patients, an association that held true in recent meta-analyses of 44 studies in children (6) and 31 in adults (7).

CAUSES OF FO

Clinically, FO is usually defined by some combination of edema, excessive weight gain, or excessively positive fluid balance in a patient that has received intravenous fluid therapy. In fact, FO is almost universally defined in such terms in clinical studies of humans (7, 8). However, some have argued that rather than focusing on development of edema as a foundational feature of fluid overload, clinicians should be more concerned about the presence

of hypervolemia (9). Hypervolemia is a state of excessive blood volume and elevated mean circulatory filling pressure (MCFP). Mean circulatory filling pressure is in turn defined as the average transmural pressure of the circulatory system when the heart and blood flow is stopped, and it is determined by blood volume and autonomic control of vascular smooth muscle. Its value is typically close to the average transmural pressure at the level of systemic post-capillary venules, and the pressure gradient between those venules and the right atrium (central venous pressure) is the driving force returning blood to the heart (10). In animals with a normally functioning heart, intravenous fluid therapy increases cardiac output primarily by increasing the pressure difference between the MCFP and the central venous pressure.

If the MCFP becomes sufficiently elevated by circulatory failure or fluid overload, the elevated venule pressure requires higher capillary pressures to maintain blood flow, and increased capillary pressure promotes fluid movement to the interstitial space. A high rate of fluid administration alone is not enough to produce FO (at least when within a clinically relevant range); development and maintenance of FO requires impaired excretion of water or abnormal function of the interstitial compartment, or both. For example, administration of 90 mL/kg of lactated Ringer's solution in 1 h to mildly dehydrated dogs produces none of the features of FO, and some features of FO seen during administration of 360 mL/kg in 1 h largely resolve within 30 min, accompanied by voiding large quantities of urine (11).

Hypervolemia secondary to impaired excretion of excess fluid may be seen in animals with heart, kidney, or liver disease, and some animals with these chronic conditions present for care precisely because they have clinical signs of FO. Organ dysfunction as a component of acute illness—for example, impaired heart and kidney function observed in some dogs with septic shock—may contribute to FO in the face of overzealous replacement fluid administration. Another factor contributing to impaired excretion of excess water is dissociation of arginine vasopressin (AVP) release from osmoregulation, a situation brought about by disorders and drugs that result in water retention, hyponatremia, and edema. As reviewed by Moritz and Ayus, the list of conditions associated with hospital-acquired hyponatremia due to excessive secretion of AVP and water retention is quite long and varied (12). Water retention is a particularly important issue during treatment of hospitalized children with hypotonic maintenance fluids, who often receive an excess of water via the commonly used Holliday-Seger formula[1] (13). Although FO is an occasional complication, neurological consequences of hyponatremia are the more serious side effects of excessive administration of hypotonic fluid to patients prone to water retention. Stimuli for excessive AVP release during inflammatory states includes an increased plasma concentration of interleukin-6, particularly during sepsis and tissue injury from trauma. Local production of interleukin-6 in response to osmotic stimuli is a physiological stimulus of hypothalamic AVP production, and elevated plasma concentrations secondary to systemic illness (sepsis in particular) appears to have similar effects on AVP production and release, independent of osmoregulation (14).

As anyone who has examined a patient with a soft tissue infection will recognize, inflammation also promotes edema in ways that are independent of volume status and AVP release. As described by Bhave and Neilson inflammatory states yield a reduction in interstitial fluid pressure by disrupting the tension of the collagen fibrils responsible for maintaining a tight interstitial matrix, increasing the compliance of the interstitial compartment (15). Under physiological conditions, interstitial fluid pressure is under local control via cellular connections to the collagen matrix through integrin receptors that are in turn linked to the cellular actin cytoskeleton. Inflammation may cause depolymerization of the cytoskeleton and break the integrin links to collagen, loosening the matrix and causing interstitial fluid pressure to fall, favoring fluid movement from the capillary.

Regardless of whether edema was initially caused by an increased MCFP or reduced interstitial pressure, once interstitial fluid volume has grown enough to increase tissue weight by more than 10–20% the compartment becomes highly compliant (16). This increase in compliance allows the interstitial compartment to accommodate large quantities of additional fluid without much of an increase in pressure, serving to maintain edema once it has begun.

In the case of edema caused by intravenous fluids administered to animals with systemic inflammation, there are also contributions from reduced plasma albumin concentration and disruption of the endothelial barrier to albumin. The dilutional effect of fluid therapy and the acute phase response to reduce plasma albumin concentration decreases plasma oncotic pressure and favors fluid filtration. The capillary glycocalyx barrier to albumin may be compromised by inflammation (17), release of atrial natriuretic peptide secondary to hypervolemia (18), and rapid fluid administration (even in the absence of increased atrial natriuretic peptide) (19). Thus, both underlying disease and the fluid resuscitation to support the circulation can favor development of edema.

WHY IS FO HARMFUL?

FO causes harm due to the effects of edema fluid in the interstitial space. In the lung, the presence of excess extravascular water impairs gas exchange, reduces pulmonary compliance, and increases the work of breathing, complications that reduce the oxygen content of blood and increase the amount of oxygen consumed by the muscles of ventilation. In the systemic circulation, FO may impair diffusion of oxygen and energy substrates, obstruct capillary blood flow and lymphatic drainage, distort tissue architecture, and impair cell-to-cell interactions. Every major organ system may manifest complications of the syndrome (**Table 1**), but the lungs and organs confined by rigid structures (brain) or capsules (kidney, liver) may be particularly vulnerable. It is important to recognize that by the time edema

[1]The original Holliday-Segar formula is 100 mL/kg/day for patients <10 kg, 1 liter + 50 mL/kg/day for patients 10–20 kg, and 1.5 L + 20 mL/kg/day for patients >20 kg. Thus, for a 22 kg patient the daily volume would be 1540 mL, or 70 mL/kg/day.

TABLE 1 | Adverse effects of FO on organ function.

Organ system	Potential complications	Examples of evidence
Brain	• Cognitive impairment • Delirium • Increased ICP/decreased CPP	• Mechanically ventilated patients with FO have longer periods of delirium/coma after extubation (20) • Cortical necrosis observed in a dog with FO (21)
Gastrointestinal tract	• Ileus • Increased permeability to bacterial translocation • Impaired liver function • Increased intra-abdominal pressure/ compartment syndrome	• Prolonged ileus is associated with FO in humans (22) • Higher wound infection rates associated with FO (23) • Strong association between resuscitation fluid and compartment syndrome (24)
Heart	• Myocardial edema • Arrhythmia • Impaired systolic and diastolic function	• Elevated troponin and pressor requirements associated with fluid resuscitation (25)
Kidneys	• Increased interstitial pressure • Decreased RBF/GFR • AKI	• Association of FO with AKI (26)
Lungs	• Pulmonary edema • Pleural effusion	• Improved lung function in patients treated with conservative fluid therapy (27)
Skin/muscle	• Edema • Weakness	• Delayed healing of abdominal wound closure (28)

can be seen and felt at the body surface it is also occurring internally. Whereas, the skin can survive prolonged periods of reduced oxygen delivery and can maintain some of its barrier function despite distorted architecture, internal organs with higher basal oxygen consumption and more complex functional architecture cannot.

DIAGNOSIS

Although FO is often first diagnosed based on recognition of edema or effusion, a better approach is to identify it earlier by monitoring changes in body weight or cumulative fluid balance. Measuring change in body weight has been considered the gold standard clinical measurement approach to monitor fluid balance in hospitalized humans since the 1970's and has been used to monitor critically ill companion animals (29, 30). However, because of the difficulty in obtaining and charting accurate weights in critically ill humans, a more common strategy is to monitor "ins and outs," that is, cumulative fluid administration vs. the sum of cumulative urine production, drainage losses, and sometimes volume estimates of diarrhea and insensible losses. This approach requires an indwelling urinary catheter or other means to accurately quantify urine production. Fluid balance is often used as a surrogate for changes in weight, but some studies in adults (31, 32) and neonates (33) have demonstrated extremely poor correlation between the two measurements. Technical reasons for the discrepancy include charting errors in recording fluid balance and inaccurate/erratic techniques used to obtain multiple weight measurements. One small study of 32 human cardiac surgery patients comparing FO to WG calculations identified 25 arithmetic errors in nursing charts, a finding that emphasizes the potential for caregiver error to interfere with even objective patient assessments (32). Other potential reasons for discrepancies include failure to accurately measure gastrointestinal losses or loss from wound or body cavity drainage, inaccurate prediction of insensible water losses, and the unpredictable rate of catabolic loss of tissue.

The advent of more widespread use of intensive care beds with built-in scales may make routine use of weight change more practical for human patients. Veterinary application of weight change assessment in critically ill patients is impeded by several factors, including the expense of purchasing and maintaining the calibration of accurate scales, the need to lift patients onto scales, and the weight effects of monitoring devices, bandages, and bladder size in patients that often weigh less than human infants. Commonly used formulas for % weight gain and % fluid overload include these:

$$\text{Weight gain (\%)} = \frac{\text{Current (or maximal) body weight} - \text{baseline body weight}}{\text{baseline body weight}} \times 100$$

$$\text{Fluid overload (\%)} = \frac{\text{Fluid intake} - \text{fluid output}}{\text{baseline body weight}} \times 100$$

The data used to populate these formulas may reflect the entire duration of hospitalization or may be used to monitor daily changes. In patients judged to be dehydrated at baseline, the formula may be modified to subtract the % dehydration (expressed in weight or volume of fluid, depending on the formula) from the numerator (34). Although there is not universal agreement on what degree of weight gain or FO represents a clinically important change, widely cited figures include 5 and 10%, with 10% marking a threshold for intervention.

The development of complications of FO probably depends not only on weight change or fluid balance, but also on the *distribution* of excess water. In critical illness there may be a variable relationship between total body water content and the compartmental distribution of water between extravascular and intravascular, and within the vascular compartment the distribution between the unstressed volume and the stressed volume that creates cardiac preload. An excess of extracellular water is more likely to produce clinical complications of FO than an excess of intracellular water. Supporting this is the observation of Bihari et al. that sodium balance—a key determinate of extracellular fluid volume—correlates better with respiratory dysfunction than does fluid balance (35).

The presence of hypervolemia has been assessed by physical exam findings, invasive hemodynamic pressure measurements, and ultrasound assessment. As reviewed by Beaubien-Souligny et al. (36), ultrasound techniques may identify hypervolemia in humans by documenting internal jugular vein distension, dilation of the inferior vena cava, reversal of systolic:diastolic hepatic vein flow, development of pulsatile portal vein flow, and discontinuous intrarenal venous flow. Ultrasound manifestations of increased intracranial pressure include an increase in the diameter of the optic nerve and a reduction in diastolic flow of the middle cerebral artery. The presence of increased extravascular lung water is revealed by an increase in the number of B lines.

Ultrasound examination is also used to identify patients that are likely to respond to intravenous fluids with an increase in cardiac output. Veterinary studies using ultrasound to predict fluid responsiveness have included assessment of caudal vena cava collapsability (37, 38) and prospective comparison of the CVC diameter to that of the abdominal aorta (38), where "fluid responsiveness" was defined as a >15% increase in ascending aorta velocity time index immediately following administration of a fluid bolus. Although the authors of a retrospective case series (37) concluded that the effect of administration of 30 mL/kg of LRS (at an unspecified rate) could be predicted by the magnitude of the respiratory effect on CVC diameter, a prospective study demonstrated that respiratory variation in CVC diameter did not predict the response to rapid (1 min) administration of 4 mL/kg of Hartmann's solution. In contrast, a ratio of the maximum CVC diameter to aortic diameter at the level of the porta hepatis of 0.83 had a sensitivity of 100% and a specificity of 75% for fluid responsiveness.

FO AS AN ENTITY IN VETERINARY PATIENTS

The author is aware of just three reports of small studies that addressed the incidence and impact of FO in dogs and cats. A retrospective study defined FO as development of symptomatic pulmonary edema or pleural effusion in 11 cats with urethral obstruction that were treated with intravenous fluids, and compared recorded data from those cats with 51 control cats that had urethral obstruction but did not develop respiratory signs (39). A "FO score" was calculated based on the % fluid overload formula (see above), and weight change between admission and the date that respiratory signs developed was calculated. Although the relationship between FO score and weight change was not described, some cats in both groups had negative fluid balance and some affected cats lost weight by the time they developed respiratory signs. Although the range of FO scores in the control cats was greater than that of the cats with FO, and included subjects with more severely negative and positive fluid balance, the median FO score in affected cats was significantly greater than the controls (6 vs. 2.46%). Ten affected cats developed a cardiac gallop, and echocardiography identified underlying heart disease in 5 of 6 cats examined; therefore, occult heart disease was likely the single most important factor in the development of clinical signs.

Another veterinary report defined FO as a positive fluid balance in dogs (after correcting dehydration) that were monitored with a closed urine collection system, and compared outcomes between 34 dogs with critical illness and 15 hemodynamically stable dogs with neuro-orthopedic disease that had closed urine collection systems in place to assist with nursing care (34). Fluid balance and % FO were examined as continuous data, and correlation with APPLE scores and survival at discharge was evaluated. Critically ill dogs had significantly greater positive fluid balance than the control group, and 8/16 dogs with substantial FO (12% or more) died. There was only a weak correlation between % FO and composite APPLE scores, which were based on clinical data that was not collected at a standardized time point and could have under- or overestimated the severity of illness.

More recently, a prospective observational study of dogs with acute kidney injury described the relationship between systemic hypertension and severity of kidney injury, and included observations about FO (40). In this report, FO was characterized as edema and was diagnosed based only on discretionary clinician assessment of acute weight gain, development of body cavity effusion, or physical examination findings. 22/52 dogs met the criteria for FO, and these dogs were significantly more likely to have hypertension and were more likely to die than dogs without.

Although these studies demonstrate potential harm of FO in clinical veterinary patients, a causal relationship between FO and outcome can't be demonstrated by a retrospective or observational study. Prospective interventional studies comparing the effect of standard (or liberal) fluid administration with fluid restriction on %FO and outcomes are needed to address this.

AVOIDING FO

Most reports of studies of FO have focused on the effect of fluid administration in the early hours to 1–2 days of treatment of life-threatening illness. Because of the growing evidence that FO is associated with worse outcomes in the critically ill, there has been considerable interest in validating non-invasive techniques to identify patients who respond to intravenous resuscitation fluid with an increase in cardiac output, and avoid (or at least limit) administration of fluids to those who do not. Those techniques are reviewed in detail by Boysen and Gommeren elsewhere in this issue; however, it is worth mentioning here that there are unresolved questions about the benefit of an increase in cardiac output immediately following a fluid bolus when that increase may be transient and yet result in longer-lasting edema. For example, Roger et al. demonstrated that of the septic patients who responded to a fluid bolus with an increase in cardiac stroke volume, half lost that benefit within 20 min (41). Most studies of techniques used to predict fluid responsiveness have not characterized patient responses beyond a few minutes, and it is quite possible that for many, a transient response to fluid infusion does not translate into a sustained benefit for circulation or outcome.

Fluid therapy does not end with initial resuscitation and in fact often continues for days in the critically ill, in stages that have been characterized as rescue, optimization, stabilization, and de-escalation (**Figure 1**) (42). During initial rescue (resuscitation), most clinical decisions about fluid therapy are made within minutes and are based predominately on clinical signs. It is common to see unambiguous signs of positive hemodynamic responses to fluid administration in overtly hypovolemic patients, and physical examination alone or sometimes in combination with the ultrasound techniques noted above is often adequate to guide fluid dose and rate of administration and avoid hypervolemia. The optimization phase occurs over hours, or longer if the underlying disease is complex or progressive, for example sepsis or pancreatitis. During this phase fluid therapy may require ongoing administration of replacement type fluids that are titrated toward optimizing the circulation but avoiding an excess that will produce edema. It is at this stage that response to fluids may become much more nuanced and difficult to evaluate with physical examination alone, and using other techniques—for example, ultrasound and measurements related to oxygen delivery—become much more important. The stabilization phase occurs during recovery when the patient has become hemodynamically stable and fluid therapy shifts toward optimizing electrolyte balance, replacing normal and pathological ongoing losses, and the beginning of a negative fluid balance as the patient excretes the excess fluid administered during resuscitation and optimization. The de-escalation phase is characterized by a transition to self-sufficiency via oral intake and a negative fluid balance where FO had occurred.

The optimization and stabilization phases are times when development of FO due to inappropriate administration of excessive quantities of both water and sodium in "maintenance" fluids and fluid vehicles for drug administration is probably common. Routine practice in charting human fluid balance ignores the volume of fluid administered as a vehicle for drugs, and this "fluid creep" can create a large volume of unaccounted fluid administration that contributes to FO. In fact, maintenance fluid and fluid creep may account for the majority of parenteral water and sodium administration in human ICU patients (43). The common veterinary practice of using a high-sodium replacement fluid like lactated Ringer's or a proprietary equivalent, at volumes that are often much larger than required to replace normal ongoing losses in an immobilized critically ill dog or cat, likely contribute a great deal to the prevalence of FO. Maintenance requirements of water and electrolytes for dogs and cats may be very different from commercial fluid composition and commonly cited administration rates, as has been recently reviewed in detail elsewhere (44).

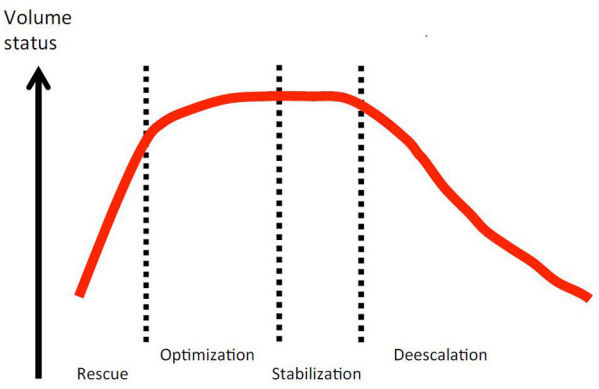

FIGURE 1 | Conceptual relationship between patient volume status and the four phases of fluid therapy in critical illness. Open access image from the Acute Dialysis Quality Initiative 12, downloaded from https://www.adqi.org/Images on 3/15/2021.

TREATMENT OF FO

The clearest indication for intervention in animals with FO is the presence of hypervolemia, which should be managed with sodium and water restriction, diuretics, and in selected life-threatening situations, hemofiltration when the potential for a diuretic response is impaired. The most obvious cases of hypervolemia include edematous animals with kidney injury causing oliguria or anuria, and animals with pulmonary edema secondary to heart failure. Physical examination alone is likely to correctly identify these and inform treatment. Diuretic treatment for left sided congestive heart failure usually consists of furosemide 1–2 mg/kg by intravenous or intramuscular injection, followed by an intravenous constant infusion (0.66 mg/kg/hour) for 6 h treatment blocks when venous catheterization can be obtained without compromising the patient (45). Animals with kidney injury and oliguria may have impaired delivery of the drug to site of action in the loop of Henle. Animals that do not respond to usual doses of furosemide (e.g., 2 mg/kg) may respond to high doses, e.g., 2 mg/kg repeated to as much as 8 mg/kg within 1–2 h, followed by a continuous infusion titrated to maintain the target rate of urine production.

Animals with other causes of FO and edema may be hyper-, normo-, or hypovolemic, and classification and treatment of these may be more difficult. For example, an animal with sepsis or pancreatitis may become edematous at a low MCFP because of changes in the microcirculation and interstitial matrix, and aggressive treatment with diuretics for imagined hypervolemia will compromise circulation and cause harm. These animals may develop relatively severe FO after even tiny increases in MCFP. If there is clinical evidence of impaired circulation that may respond to fluid therapy, benefit from resuscitation fluids should be predicted and monitored with adjunct assessment methods such as ultrasound measurement of dynamic variables, central or mixed venous oxygen saturation, and central venous or arterial blood pressure responses to incremental doses of fluids or drugs. Replacement fluids should be used only during the resuscitation and optimization phases, with an eye toward discontinuing them as soon as a transition to the stabilization phase is possible. Albumin solutions or plasma may be administered to animals with hypoalbuminemia that is sufficiently severe to contribute to edema formation. Although administration of albumin solutions instead of crystalloids to critically ill humans provides little improvement in most

outcome measures, those patients generally require less total fluid for resuscitation/optimization and may have less tendency for FO (46–48). We have observed similar benefit from albumin or plasma administration to critically ill dogs in our ICU, reaching the stabilization phase with less tendency for FO. Although fresh frozen plasma is an inefficient way to provide albumin, some animals may benefit from coagulation factors or other plasma components. In our ICU, a common dosing strategy for animals in shock from sepsis and other causes of a systemic inflammatory response is to use plasma (and more recently, 5% canine albumin) as a component of resuscitation fluid therapy, then continue administration as a continuous rate infusion of ∼20 mL/kg/day during the optimization phase. This fluid is always accounted for in total fluid balance calculations, and crystalloid administration is reduced by an equal amount.

Animals in septic shock are rarely resuscitated with fluid therapy alone. Removal of the underlying cause, for example infection source control, is a critical step to reversing pathology of the microcirculation and interstitial matrix to correct FO. Mechanical ventilation to reduce the work of breathing and decrease pulmonary shunt may be required to address an increase in extravascular lung water. Pharmacological management of the circulation, for example the administration of pressors to maintain MCFP, arterial pressure, and cardiac output, is routinely essential to correct hypotension restore adequate oxygen delivery and allow earlier transition to a stabilization phase with less fluid administration.

Once an animal with FO edema has reached the stabilization phase it may be much more tolerant of fluid restriction and graded diuretic therapy. In this stage, a low test dose (<1 mg/kg) of intravenous furosemide may be administered and the patient response evaluated. If urine output increases the patient is monitored for evidence of hypovolemia, and in its absence diuretic therapy may be continued with a goal of gradually reducing FO to <5% over 1–2 days. Fluid therapy at this stage is often provided partly or wholly via enteral nutrition, but if intravenous fluid is continued it should be restricted to water and electrolytes calibrated to meet metabolic need (44). By the time the animal reaches the de-escalation phase they are often capable of ambulation and spontaneous position change; this activity may hasten elimination of FO.

CONCLUSION

Fluid overload is likely to be a detrimental and sometimes life-threating complication of disease that is much more likely to occur when fluid therapy is not carefully calibrated to maintain an adequate circulation without causing edema. It is clearly much better to avoid it in the first place rather than treat it after it appears. This is best accomplished by administering replacement fluids only to those patients capable of responding with an increase in oxygen delivery during the rescue and optimization phases of fluid therapy, and by using a protocol for maintenance fluid that is guided by careful consideration of the actual metabolic needs of the animal.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Assessment of Volume Status and Fluid Responsiveness in Small Animals

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Intravenous fluids are an essential component of shock management in human and veterinary emergency and critical care to increase cardiac output and improve tissue perfusion. Unfortunately, there are very few evidence-based guidelines to help direct fluid therapy in the clinical setting. Giving insufficient fluids and/or administering fluids too slowly to hypotensive patients with hypovolemia can contribute to continued hypoperfusion and increased morbidity and mortality. Similarly, giving excessive fluids to a volume unresponsive patient can contribute to volume overload and can equally increase morbidity and mortality. Therefore, assessing a patient's volume status and fluid responsiveness, and monitoring patient's response to fluid administration is critical in maintaining the balance between meeting a patient's fluid needs vs. contributing to complications of volume overload. This article will focus on the physiology behind fluid responsiveness and the methodologies used to estimate volume status and fluid responsiveness in the clinical setting.

Keywords: dogs, cats, fluid responsiveness, volume status, dynamic, static, POCUS, wet lung

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INTRODUCTION

Although the route of administration is not always specified within this review, it should be presumed all references to fluids refer to intravenous (IV) administration unless otherwise stated. In hemodynamically unstable patients, IV fluids are administered to increase cardiac output (CO) and improve tissue perfusion (1). However, in humans, cats, and dogs both insufficient and excessive IV fluid administration are associated with increased morbidity and mortality (2–8). In human medicine, recommendations have historically focused on the rapid and efficient administration of fluids (referred to as "fluid loading"), however, over the past few decades mounting evidence has demonstrated the negative effects of overzealous fluid therapy ("fluid overload") (5, 6, 9–12). As a result, a clear distinction between two important aspects of fluid resuscitation has recently emerged: (1) assessment of volume status and (2) assessment of fluid responsiveness. Volume status attempts to determine if a patient's circulatory volume is decreased, normal, or increased at a static point in time. Volume responsiveness on the other hand considers a dynamic question; will additional fluid administration lead to an increase in stroke volume (SV) and hence CO. This review offers an overview of the pathophysiology and monitoring of fluid administration, with an emphasis on fluid responsiveness.

FLUID RESPONSIVENESS

A consensus on the exact definition of fluid responsiveness is lacking. In general, it can be considered an attempt to identify patients who will have a positive physiologic response to fluid administration. More precisely it can be defined as *"the positive reaction of a physiologic parameter of a certain size to a standardized volume of a certain type of fluid (or other type of induced preload change) within a certain amount of time and measured within a certain interval"* (13). Unfortunately, defining fluid responsiveness is complicated by a lack of consensus regarding the ideal physiologic parameter(s) to measure, the degree of change in the measured physiologic variable that defines a positive response, what defines a preload challenge, and if an IV fluid bolus is used as the preload challenge, the amount of fluid that defines a standardized volume. In general, the physiologic parameter measured can be classified as either static or dynamic depending on how it is measured, which is explained in detail in section Defining Static vs. Dynamic Markers below. In both the human and veterinary literature, the magnitude of change (increase or decrease) that constitutes a positive response varies from 6 to 36% depending on the physiologic parameter measured and conditions under which the preload challenge is induced (14–27). In general, there is a trend to define a positive fluid responder as any patient that has an increase in a measured dynamic marker, such as CO, by $\geq$10–15% following a preload challenge (14, 16, 25, 28–30). There are generally two ways to induce a preload challenge; (1) by directly increasing the vascular volume through a traditional or a mini IV fluid bolus, or (2) shifting fluids within the vascular system without actually changing the patients total vascular volume. The latter is accomplished through maneuvers such as passive leg raising (PLR), or by assessing the effect of inspiratory and expiratory pressures on venous return (VR). PLR maneuvers, which are often used in human ICU patients, shift blood from the periphery to the central circulation increasing VR without actually administering fluids to the patient (26, 29). Although PLR maneuvers have been investigated in anesthetized swine, research on its application in cats and dogs is lacking (31). Manipulating respiratory pressures in patients receiving positive pressure ventilation influences heart-lung interactions (see **Figures 1A–C**), which can impact VR without changing the total circulating blood volume (26, 29). These concepts are discussed in greater detail in section Fluid Bolus, Mini Bolus, Heart-Lung Interactions and Passive Leg Raising. In the veterinary clinical setting, a preload challenge is most often elicited through a traditional IV fluid bolus, typically described as isotonic fluids at a dose of 10–20 mL/kg administered over a period of 10–15 min in both cats and dogs (14, 32–34). More recently, and in many veterinary research settings, a mini fluid bolus which is often defined as 3–5 ml/kg IV isotonic fluid administered over 1 min (15, 16, 20, 23, 35) has been used to induce a preload challenge. However, in clinical practice there will be considerable variation in the volume of fluid administered because of clinician preference, patient characteristics such as species and age, the type of fluid used, and the underlying disease process. Regardless of what techniques are used the goal of fluid responsiveness is to determine if a patient will benefit from additional IV fluid administration while minimizing the risk of fluid overload. Therefore, fluid responsiveness can be summarized as the presence or absence of a positive measurable reaction following the administration of a precise preload challenge.

To understand fluid responsiveness, it is important to differentiate the concepts of fluid loading and a preload challenge. Fluid loading is the rapid administration of IV fluids for suspected hypovolemia, often in the absence of monitoring a real time response to fluid administration (13, 36, 37). It is most often applied in the emergency and critical care (ECC) setting when confronted with severe life-threatening hypotension and hypoperfusion secondary to overt hypovolemia. In contrast, a preload challenge is a test of the cardio-circulatory system designed to assess if a patient has preload reserve that will increase CO with additional IV fluid administration (fluid responsiveness) (36). It allows more individualized patient fluid therapy, which may be preferred over protocolized therapy in some settings (36).

Although volume status and fluid responsiveness are often considered simultaneously, they should be evaluated independently in individual patients. Many hypovolemic patients require fluid bolus resuscitation to improve tissue perfusion and reverse the potentially fatal consequences of shock. In the human intensive care unit (ICU) setting, 20% of patients receive resuscitation fluids, with this number increasing to >30% on the first day of ICU admission (1). Results are likely similar or even higher in veterinary ICU patients. Common reasons for administration of bolus fluid therapy include reversal of severe hypovolemia, sepsis, large perioperative volume losses, hemodynamic derangements and oliguria that is volume responsive (32, 38, 39). Although the number of ICU patients receiving bolus fluid resuscitation has remained fairly constant over the past decade, the rationale for initiation of IV fluid bolus therapy has shifted in human ICUs; more patients are receiving therapy in response to signs of impaired tissue perfusion or a measured decrease in CO, with fewer patients receiving therapy in response to abnormal vital signs in the absence of signs of abnormal perfusion (1). This emphasizes a paradigm shift away from "a one size fits all" and the practice of "volume loading," to establishing "euvolemia" and an "optimal fluid balance," particularly in patients with systemic inflammation or sepsis.

Merely assessing volume status does not predict a patient's response to fluid loading. A patient may be hypovolemic and non-fluid responsive due to the complex interaction of the glycocalyx, vascular permeability, capillary leak, vascular tone, and cardiac function. At the same time, the fact that a patient is fluid responsive does not always imply hypovolemia is present. For example, healthy euvolemic patients given a fluid bolus may meet the definition of being fluid responsive. Finally, a patient that is hypovolemic and fluid responsive may still develop complications of volume overload, particularly if increased vascular permeability is present (40, 41). For example, due to pre-existing or fluid induced endothelial dysfunction, it is reported that within an hour <5% of a fluid bolus remains within the

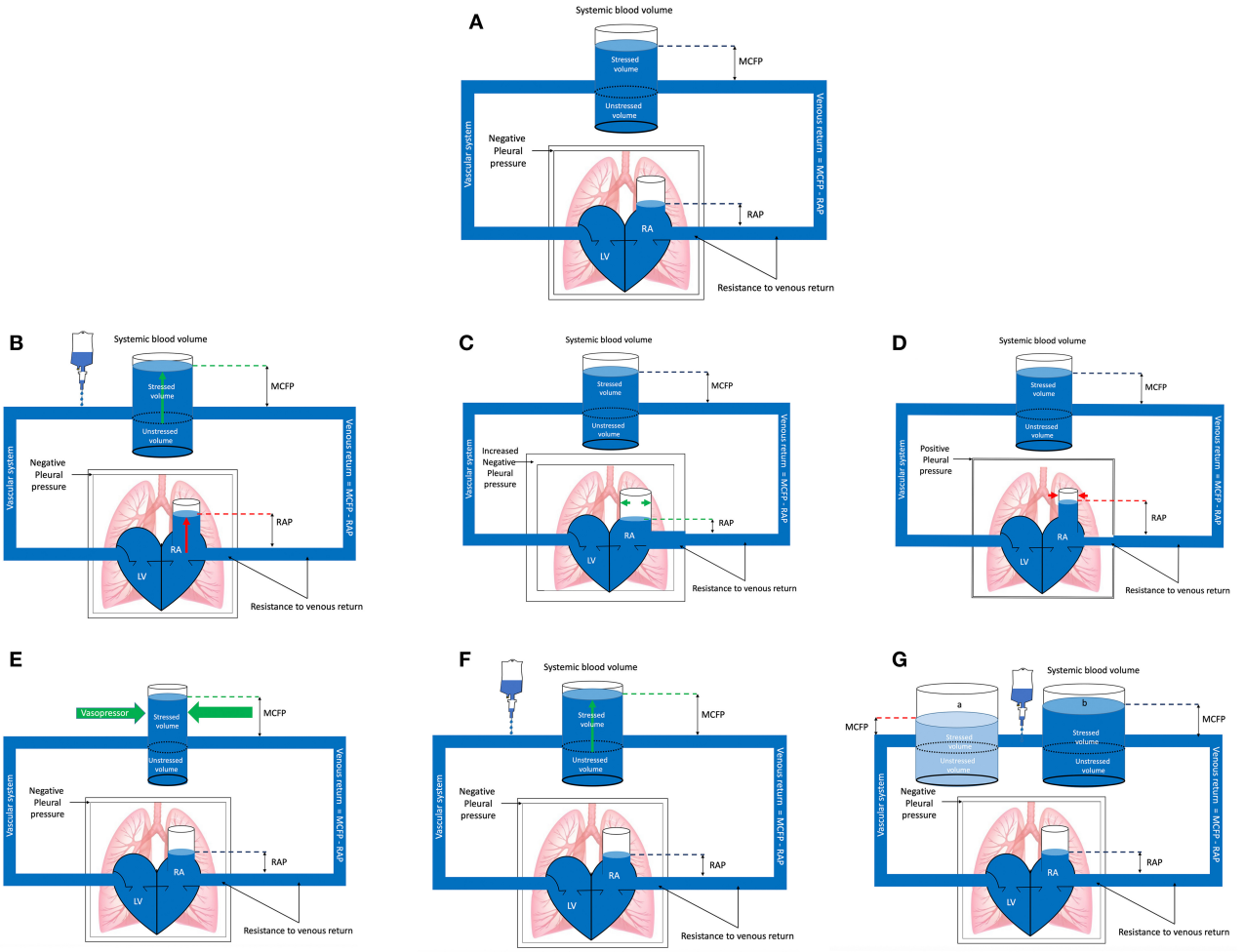

FIGURE 1 | (A) Baseline. The pressure gradient between the right atrium (RA) and mean circulatory filling pressure (MCFP) determines venous return (VR) or preload. The veins are capacitance vessels. The blood volume contained within the venous system that does not contribute to pressure or stress being applied to the vessel wall is referred to as the unstressed volume. This unstressed blood volume depends on vessel size (and thus venoconstriction or -dilation). Any additional blood volume added to the venous system beyond the unstressed volume will exercise a force on the wall of the vein, distending it, thus generating a transmural pressure above zero. This additional blood volume is referred to as the stressed volume and is the main contributor to MCFP. Also depicted is the negative pleural pressure which changes during the respiratory cycle and influences the heart and VR, referred to as heart-lung interactions. RAP, right atrial pressure; LV, left ventricle. **(B)** Spontaneous inspiration. In the spontaneously breathing patient negative pleural pressure increases during inspiration, decreasing the resistance to venous return (VR) and the right atrial pressure (RAP). This results in a greater difference between the mean circulatory filling pressure (MCFP) and RAP, subsequently increasing VR or preload. The opposite effect occurs during expiration. All other factors held constant, the magnitude of the effect and impact on VR will vary depending on the volume status of the patient: The more hypovolemic the patient is, the greater the result of heart-lung interactions on VR. RA, right atrium; LV, left ventricle. **(C)** Mechanical inspiration. During the inspiratory phase of positive pressure ventilation the pleural pressure rises (becomes less negative) which increases the resistance to venous return and directly compresses the right atrium, increasing the right atrial pressure (RAP). This results in a decrease in the difference between the mean circulatory filling pressure (MCFP) and RAP, subsequently decreasing venous return (VR) or preload. The opposite effect occurs during expiration. All other factors held constant, the magnitude of the effect and impact on VR will vary depending on the volume status of the patient: The more hypovolemic the patient is the greater the result of heart-lung interactions on VR. RA, right atrium; LV, left ventricle. **(D)** Vasopressor administration. Administration of a vasopressor causes vasoconstriction which, all other factors held constant, may result in an increase in the stressed blood volume relative to the unstressed blood volume, depending on the type of vasopressor administered (arterial, venous or mixed). The increase in stressed volume will increase the mean circulatory filling pressure (MCFP), increasing venous return (VR). This partly explains the improvement in cardiac output (CO) sometimes seen with vasopressor administration. However, because vasopressors will also increase resistance to venous flow (increase not illustrated in this diagram), vasopressors may only cause a minimal increase in VR. RAP, right atrial pressure; RA, right atrium; LV, left ventricle. **(E)** Fluid loading, fluid responsive. For fluid loading to be effective it must increase the stressed volume more than it increases right atrial pressure (RAP). In this illustration fluid loading has caused a larger increase in the stressed volume with minimal increase in RAP. Therefore, the mean circulatory filling pressure (MCFP) increases while the RAP is minimally increased, and the result is an increase in venous return (VR). Understanding the Frank Starling curve helps explain if the stressed volume increases more than the unstressed volume or RAP. RAP, right atrial pressure; RA, right atrium; LV, left ventricle. **(F)** Fluid loading, fluid unresponsive. In this example a fluid bolus is administered which increases the stressed blood volume and mean circulatory filling pressure (MCFP), however, at the same time there is a parallel increase in right atrial pressure (RAP). The net results is a failure of venous return (VR) and subsequently cardiac output (CO) to increase (fluid unresponsive). Given organ blood flow is driven by the difference between MAP and central venous pressure (CVP), and that CVP becomes the major factor determining organ and microcirculatory flow when MAP is within an organ autoregulatory range, an increase in CVP may contribute to organ injury. **(G)** Fluid loading, fluid unresponsive: In

(Continued)

FIGURE 1 | this example, all other factors held constant, vasodilation causes an increase of the unstressed blood volume relative to the stressed volume [**(a)**, light blue], which decreased the mean circulatory filling pressure (MCFP) (red dotted line). All other factors held constant, fluid loading **(b)** increases the stressed volume and returns the MCFP to baseline (blue dotted line) but has failed to increase cardiac output (CO) because insufficient fluids have been administered to increase MCFP above baseline. With vasodilation the proportion of unstressed volume increases relative to the stressed volume, resulting in a greater volume of fluid needing to be administered before a significant increase in the stressed volume is noted. The right atrial pressure (RAP) will also change with alterations in the stressed blood volume and vasodilation, which has not been illustrated here for simplicity. Changes in vascular tone because of fluid loading are also not shown for simplicity. Understanding the Frank Starling curve helps explain if the stressed volume increases more than the unstressed volume or RAP. RA, right atrium; LV, left ventricle.

IV space of some human patients with sepsis (41). In patients that are predisposed to volume overload the prediction of fluid responsiveness is vital in trying to determine if inotropic and/or vasopressor support is preferred over fluid replacement.

Given there is a lack of data regarding evidence-based fluid management in hypotensive human and veterinary ECC patients it is not surprising there is considerable heterogeneity in the way IV fluids are administered in shock states, including the criteria used as triggers, targets, volume, and safety limits for fluid input (31, 36, 39, 42). Much of the heterogeneity likely stems from diverse backgrounds of professionals involved in initial resuscitation, a clear lack of evidence-based guidelines, the different pathophysiological processes causing hypotension, and the reliance on simple clinical physiological variables to estimate fluid responsiveness. The remainder of this article will explain the pathophysiological processes of fluid responsiveness, after which monitoring tools for volume status and fluid responsiveness will be discussed, and the heterogeneity in how fluid responsiveness is assessed in veterinary medicine will be highlighted.

THE (PATHO)PHYSIOLOGY OF FLUID RESPONSIVENESS

Understanding circulatory physiology and pathophysiology helps understand how different scenarios mandate different therapeutic and fluid management strategies. Two general assumptions are expected in response to a preload challenge; (1) increased venous volume leads to increased cardiac preload (venous loading = cardiac loading), (2) increased preload leads to increased stroke volume/cardiac output (VR = CO).

Mean Circulatory Filling Pressure: Increased Venous Volume Leads to Increased Cardiac Preload (Venous Loading = Cardiac Loading)

It may seem intuitive that an IV fluid bolus will lead to increased VR. However, a clear understanding of circulatory physiology may explain why increased VR is not always observed.

Preload, or VR, is determined by the pressure gradient between capacitance veins and the right atrium (RA). The pressure within the capacitance veins is termed mean circulatory filling pressure (MCFP) (13, 29, 30). The venous system is composed of highly distensible capacitance veins, which contain the majority of blood volume (13, 29). These capacitance veins require a minimal volume of blood to prevent them from collapsing, which occurs if transmural pressure becomes negative. This "minimal" blood volume to prevent collapse depends on vessel size (and thus venoconstriction or -dilation) and is referred to as the unstressed volume; it is any blood volume that can be added to the venous system that does not contribute to pressure or stress being applied to the vessel wall above a transmural pressure of zero (13, 29, 30). Note that venous pressure is the pressure created by venous blood against the wall of the vein (intraluminal) regardless of the pressure surrounding the vessel, while transmural pressure is the difference in pressure across the wall of a vessel (within the vessel and outside the vessel). Any additional blood volume added to the venous system beyond the unstressed volume will exercise a force on the wall of the vein, distending it, thus generating a transmural pressure above zero (13, 29, 30). This additional blood volume is referred to as the stressed volume and is the main contributor to MCFP (**Figure 1A**) (29). Think of a horizontally placed water-filled balloon, in which you create a tiny hole in one end. The water will leak out of the balloon until the transmural pressure becomes zero, however, there will still be a residual amount of water present inside the balloon. This amount of fluid, which does not stretch the wall of the balloon above a transmural pressure of zero, would be considered unstressed volume and does not contribute to fluid movement out of the balloon. The volume of water that poured out of the balloon was the stressed volume, as it stretched the wall of the balloon creating a force (transmural pressure above zero) that acted to move fluid out of the balloon.

MCFP [or mean systemic pressure (MSP)] varies with changes in venous blood volume or vessel tone, which determines the balance of venous blood contained within the unstressed and stressed blood volume. As a consequence, MCFP may only be increased by changes in blood volume, or by changes in vessel tone (**Figures 1D–G**) (29). This partly explains the improvement in CO sometimes seen with vasopressor administration (29).

MCFP is predominantly regulated by the effects of the sympathetic nervous system on the splanchnic venous system (43). Depending on the species, the splanchnic venous system contains 20–30% of the total blood volume, is 30 times more compliant than the arterial circulation, and is heavily innervated with α-adrenoceptors (43). It serves as a reservoir of blood contained within capacitance vessels which can easily change in volume to maintain VR to the heart (13).

MCFP, right atrial pressure (RAP) and the resistance to venous flow (Rv) are the main driving forces of VR as expressed through the following formula: VR = [(MCFP – RAP)/Rv], (**Figure 1A**) (13). This formula implies VR can be increased by one of 3 mechanisms; (1) lowering RAP, (2) decreasing Rv, or (3) increasing MCFP (**Figures 1B–G**).

From a physiologic standpoint, given VR is determined by the pressure gradient between capacitance veins and the right atrium, decreasing the right atrial pressure should increase VR, provided all other variables are held constant. However, techniques to decrease RAP are limited, and if RAP falls too low, venous collapse at the thoracic inlet may occur (13). Venous collapse causes an increase in Rv and subsequently a decrease in VR. Therefore, in the clinical setting it is generally not practical to decreases RAP.

Resistance to venous flow may be decreased by increasing venous compliance through venodilation (35). However, venodilation results in an increase in the ratio of the unstressed to stressed blood volume and a subsequent decrease in MCFP. Therefore, depending on the relative changes in the Rv and MCFP, the net effect on VR is uncertain.

MCFP can be increased through venoconstriction or fluid loading (**Figures 1D,E**) (13, 29, 44, 45). Venoconstriction, because it will increase Rv, may only cause a minimal increase in VR. Fluid loading is therefore often used to try and increase VR, however, for fluid loading to be effective it must increase the stressed volume to a greater degree than it increases the RAP (**Figure 1E**) (45). Fluid loading may fail to increase CO when: (1) patients' have a parallel increase in RAP and MCFP (**Figure 1F**), (2) MCFP fails to increase due to inadequate volume being administered to vasodilated patients (**Figure 1G**), and (3) patients are preload unresponsive (on the flat portion of Frank-Starling curve (**Figure 2A**) (36, 45). Organ blood flow is driven by the difference between mean arterial pressure (MAP) and RAP in contrast to VR which is driven by the difference between MCFP and RAP. Therefore, any increase in RAP can contribute to decreased organ blood flow if MAP remains constant. Given RAP is the major factor determining organ and microcirculatory flow when MAP is within an organ's autoregulatory range, an increase in RAP may contribute to organ injury (45). Understanding the Frank-Starling curve helps explain what might occur if the stressed volume increases more than RAP.

Frank-Starling and Marik-Philips Curve: Increased Preload Leads to Increased Stroke Volume/Cardiac Output (Venous Return = Cardiac Output)

The Frank-Starling curve (**Figure 2A**) describes the relationship of preload and SV, which subsequently determines CO and oxygen delivery (DO_2) to the tissues. The relationship between these parameters can be expressed through the following 2 formulas: (1) $DO_2 = CaO_2 \times CO$, and (2) $CO = HR \times SV$. Moreover, $MAP = CO \times SVR$.

Where DO_2 is oxygen delivery (mL/min), CaO_2 is the arterial oxygen content (mL/dL), CO is cardiac output (mL/min), HR is heart rate (beats/min), SV is stroke volume (mL), MAP is mean arterial pressure (mmHg), and SVR is systemic vascular resistance (dynes/seconds/cm^{-5}).

Stroke volume is the amount of blood ejected from the heart with each beat and is dependent on preload (end-diastolic wall tension), contractility and afterload (end-systolic wall tension). According to the Frank-Starkling curve, within certain limits an increase in VR will lead to an increase in preload (29). This increased preload leads to stretching of the myocytes, which subsequently contract more forcefully, leading to an increase in SV (Frank-Starling law). *This is the foundation for the concept of fluid responsiveness*.

For a patient to be fluid responsive both the right and left ventricles must be functioning on the steep part of the Frank-Starling curve (wherein increased filling improves CO, without any major changes in other determinants of CO, such as contractility, afterload and diastolic dysfunction) (29).

Cardiac contractility can be affected by a variety of processes, fluid overload and myocardial hibernation to name a few. During fluid overload, myocytes get stretched beyond a certain level, rendering them unable to contract more forcefully, with SV subsequently failing to increase any further (fluid "unresponsiveness"). At this point fluid administration is likely to increase the stressed volume and thus MCFP, but to a lesser extent than it increases RAP, leading to volume overload (**Figures 2A–C**) (44). In addition, many critically ill human patients, and most likely a proportion of companion animals, have significant changes in cardiac contractility (e.g., due to acidosis, sepsis, etc.) placing them on the flat portion of the curve. Finally, an increase in afterload (e.g., due to vasoactive agents) can also decrease CO (44).

The Marik-Philips curve describes the relationship between increasing preload and extravascular lung water (EVLW). When the Marik-Philips curve is superimposed over the Frank-Starling curve the risk of a patient developing edema during fluid loading is nicely illustrated (**Figure 2B**) (45). A patient located at the left of the curve (the steep portion of the Frank Starling curve), has low preload prior to fluid therapy, and is very likely to be fluid responsive. This implies a fluid bolus would increase preload, leading to an increase in CO. At the same time, according to the Marik-Philips curve, this increase in preload would not be associated with a significant increase in EVLW (45). A patient located on the right side of the curve (the flat portion of the Frank-Starling curve), has a relatively high preload prior to fluid therapy. Providing an additional fluid bolus will have little to no effect on preload, and thus no improvement in SV, but is likely to have a significant increase in EVLW.

It should be remembered that every patient has its own unique set of individual Frank-Starling and Marik-Philips curves, and that these curves are influenced by factors associated with specific disease states. Knowing the factors that govern these equations will allow the clinician to estimate the effect of fluid administration, but should never be considered an absolute certainty.

The underlying cause of shock will influence an individual patient's Frank-Starling and Marik-Philips curves, and subsequently fluid responsiveness. The incidence of hypotension in hemodynamically unstable human ICU patients is as high as 33%. Considering Weil's classification of shock, it is reported in humans that 62–71% of cases are due to septic shock, 16% cardiogenic, 16% hypovolemic, 4% other distributive shock, and 2% obstructive shock (46). In contrast, the incidence of hypotension due to sepsis in small animal ICU patients, although

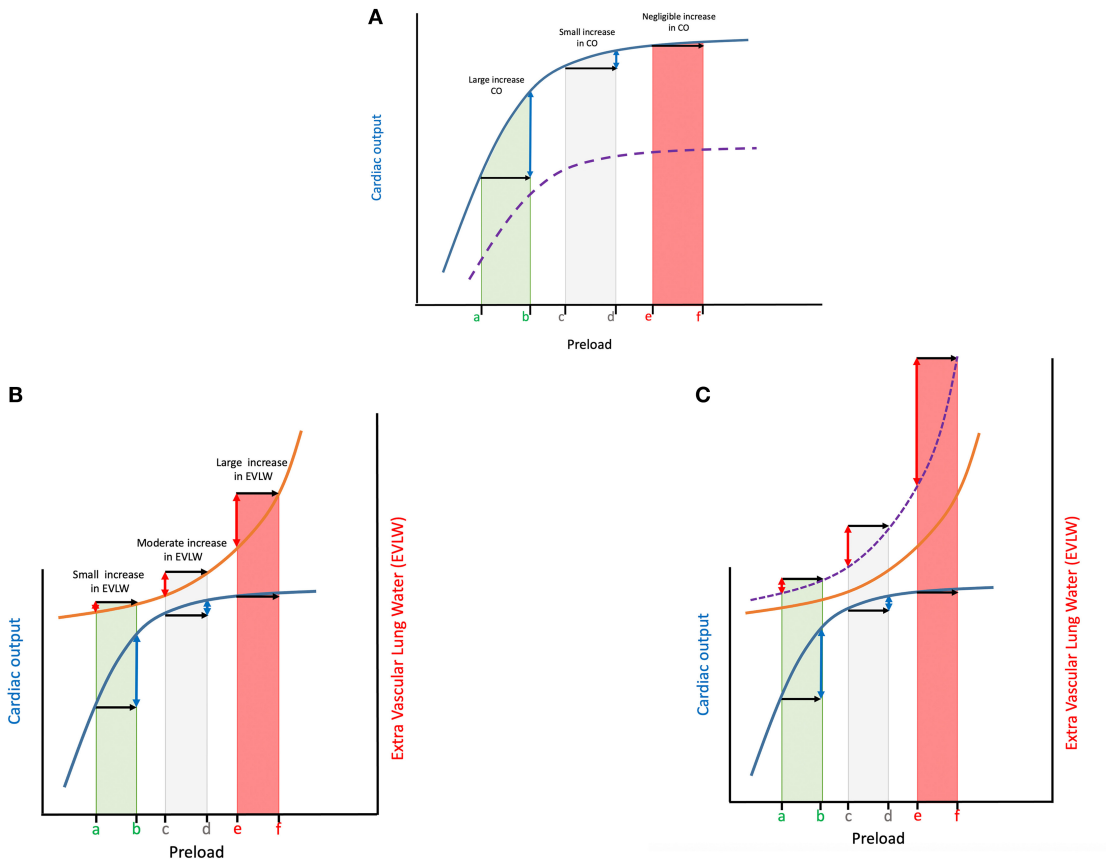

FIGURE 2 | (A) The Frank Starling curve is shown in blue for 3 different patients with a similar Frank-Starling curve (blue line), yet located at different points along that curve; The x axis shows an induced increase in preload (e.g., fluid bolus) of the same magnitude for all 3 patients (black arrows). As a result of the shape of the curve the change in cardiac output (CO) depicted on the y-axis (blue double-headed arrows) is very different depending on the point along the curve the patient is located. Patient a-b has a very large increase in CO relative to patient c-d (minimal increase in CO) or patient e-f (negligible change in CO). In patient a-b the increased preload leads to stretching of the myocytes, which subsequently contract more forcefully, leading to an increase in CO. For a patient to be fluid responsive both the right and left ventricles must be functioning on the steep part of the Starling curve. Many critically ill human patients, and most likely a proportion of our companion animals have significant changes in cardiac contractility (e.g., due to acidosis, sepsis, etc.), flattening the curve and shifting it to the right (purple dotted line), placing them on the flat portion of the curve and decreasing the rise in CO for a similar rise in preload. **(B)** The Marik-Philips curve (orange line) is superimposed on the Frank-Starling curve (blue line) to show the relationship between preload changes, cardiac output (CO) and extravascular lung water (EVLW). A patient located at the left of the curve (patient a-b), is on the steep portion of the Frank-Starling curve, has low preload prior to fluid therapy, and is very likely to be fluid responsive. This implies a fluid bolus would increase preload (black arrow), leading to an increase in CO (blue double-headed arrow). At the same time, according to the Marik-Philips curve, this increase in preload would not be associated with a significant increase in extravascular lung water (EVLW; red double-headed arrow). A patient located on the right side of the curve (patient e-f), has a relatively high preload prior to fluid therapy. Providing an additional fluid bolus to increase preload the same amount as patient a-b will have little to no effect, with no improvement in CO, but a very significant increase in EVLW. Between patient a-b and e-f is the "gray zone" where it is far more difficult to predict the impact of fluid boluses on preload, CO and EVLW (patient c-d). See text regarding gray zone effect. **(C)** The Marik-Philips and Frank-Starling curve for patients in septic shock where the Frank-Starling curve is flattened and reaches a plateau more quickly (not shown) while the Marik-Phillips curve is shifted to the left (purple dashed line) due to changes in vascular permeability, lung compliance, glycocalyx derangements, etc. Septic shock patients are more often located on the flat portion of the Frank-Starling curve and the steeper portion of the Marik-Phillips curve (patient e-f), particularly following initial fluid resuscitation. These patients are more likely to benefit from vasopressors and positive inotropes as additional fluid boluses to increase preload (black arrows) will not increase cardiac output (CO) (blue double-headed arrows) and will likely lead to volume overload and increased extravascular lung water (EVLW) (double-headed red arrows). This is because of the curvilinear shape of the left ventricular pressure-volume curve and the result of altered diastolic compliance at higher filling pressures. As atrial pressure increases, venous and pulmonary hydrostatic pressures increase, resulting in the release of natriuretic peptides. These natriuretic peptides will cause fluids to shift from the vascular space into the interstitial space. The shift of fluids to the interstitial space results in pulmonary and peripheral tissue edema. Septic patients have a higher tendency to accumulate EVLW (shift of Marik-Phillips curve to the left), and thus fluid administration should be titrated more carefully in such patients.

not well-documented, appears lower. A canine study of 35 dogs listed causes of hypovolemia (46%) more commonly than causes of sepsis (29%) in dogs with confirmed hypotension (32). Similarly, a feline study of 39 cats with hypotension found cases with suspected hypovolemia (renal or urinary disease 21%, gastrointestinal disease 13%) to be more frequent than cases with suspected sepsis, which was only documented in a small percentage of cases (39). As the Frank-Starling and Marik-Philips curves are very different between hypovolemic and septic patients, the clinical question asked (volume status or

fluid responsiveness) will be impacted by the type and severity of shock.

Hypovolemic shock patients are usually located on the ascending portion of the Frank Startling curve (fluid responders). These patients are likely to benefit from fluid administration. Administration of fluid boluses will increase SV, which typically results in improved clinical cardiovascular parameters such as HR and MAP. At the same time, their Marik-Philips curve will not be as steep, and the administered fluid boluses are unlikely to cause a dramatic increase in EVLW (**Figures 2B,C**). This combination results in a clinical scenario where the safety margins are relatively large (45). However, monitoring volume status is still recommended in patients presenting with hypovolemic shock that initially respond to fluid resuscitation, as research in humans suggests patients with persistent parameters indicative of hypovolemia, despite normalization of blood pressure and vital signs, may be at increased risk of relapsing into a state of shock (47).

Septic shock patients are more often located on the flat portion of the Frank-Starling curve (non-fluid responders), particularly following initial fluid resuscitation. These patients are more likely to benefit from vasopressors and positive inotropes as additional fluid boluses will not increase SV and will likely lead to volume overload and increased EVLW (45). This is because of the curvilinear shape of the left ventricular pressure-volume curve and the result of altered diastolic compliance at higher filling pressures. As atrial pressure increases, venous and pulmonary hydrostatic pressures increase, resulting in the release of natriuretic peptides. These natriuretic peptides, along with the increased hydrostatic pressure, will cause fluids to shift from the vascular space into the interstitial space. The shift of fluids to the interstitial space results in pulmonary and peripheral tissue edema. Tissue edema contributes to decreased oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage and disturbs cell-cell interactions. Septic patients have a higher tendency to accumulate EVLW, and thus fluid administration should be titrated more carefully in such patients. With sepsis, not only are patients less likely to be fluid responsive, but the Marik-Philips curve is also shifted to the left, further increasing the risk of volume overload and increased EVLW (**Figure 2C**) (45).

As the majority of ECC veterinary patients have non-distributive hypovolemic shock, they are more likely to respond to volume resuscitation (32, 39) and less likely to experience volume overload than human ICU patients in shock (46). In contrast, the majority of hypotensive human ICU patients have distributive septic shock with complex hemodynamic derangements that can significantly affect homeostasis of the cardiovascular system (e.g., low oncotic pressure, decreased glycocalyx integrity, increased permeability, vasodilation, etc.) (46). This may partially explain why hypotensive dogs are more likely to respond to fluid bolus therapy than human ICU patients.

Roughly 50% of preload challenges performed in critically ill human patients do not result in an increase in CO or SV, exposing these patients to the potential harm of fluid overload (48). Research regarding fluid responsiveness in small animals is sparse. A single center retrospective study consisting of 35 dogs demonstrated 60–65% of dogs that present to the ECC service with hypotension (Doppler blood pressure < 90 mmHg) will respond to fluid bolus therapy, defined as normalization of blood pressure (32). Although response in hypotensive dogs did not vary with the underlying cause, sample size was small and the sensitivity of using normalization of blood pressure (a marker of volume status rather than of fluid responsiveness), may have failed to detect some fluid responsive dogs. The actual value of hypotensive dogs responding to fluids may be higher or lower than 65% depending on what physiologic parameters are measured and how a response to fluid therapy is defined. Larger prospective canine and feline studies are required to further explore these findings.

A major clinical challenge that all veterinarians must address when confronted with a hemodynamically unstable patient is to successfully identify patients that will increase CO in response to fluid therapy (fluid responsive) vs. those who will develop adverse events from unnecessary administration of IV fluids (non-fluid responsive). The previous paragraph indicates not every patient, human or veterinary, will be a fluid responder. In severely hypovolemic patients additional fluid boluses have a high benefit to risk ratio (as stated above, volume status is the focus over fluid responsiveness in the resuscitation phase of fluid therapy). Conversely, additional fluid boluses will be detrimental in markedly hypervolemic patients. Between the extremes of severe hypovolemia and marked hypervolemia, predicting if the patient will benefit from fluid therapy without developing complications of fluid overload (e.g., the patient is fluid responsive and fluid tolerant) is more challenging. Answering whether an additional fluid bolus will be beneficial (improve CO) or not (cause volume overload) with 100% accuracy is not always possible. The gray-zone approach, which is a form of statistical analysis, suggests a "three level decision tree" when assessing if a patient might be fluid responsive or not: "Yes—Maybe—No." The gray-zone approach can be calculated for any physiologic parameter used to assess a patient's response to a preload challenge (e.g., heart rate, CO, SV, etc.). More specifically, it is defined as the interval of values (for the physiologic parameter assessed) between a sensitivity or specificity lower than 90% to classify patients as fluid responders or non-responders (16, 17, 19). The further from the gray zone a measurement lies, the greater the confidence of accurately classifying the patient as a fluid responder or not. Values within the gray zone do not allow the patient's response to a preload challenge to be determined with a high degree of confidence. When a patient lies within the gray-zone, meaning it is not easy to determine if the parameter assessed will predict fluid responsiveness, other available clinical parameters should be assessed to guide fluid strategies, ideally performed serially to track changes over time.

ASSESSING FLUID RESPONSIVENESS

Defining Static vs. Dynamic Markers

Static markers, such as central venous pressure (CVP), MAP, inferior vena cava (IVC) diameter, and end-diastolic ventricular area (LVEDA) are measures of pressure and/or volume that estimate the amount of fluid in the entire cardiovascular system

at a specific point in time. They are intended to assess volume status and are most useful as "alarm" signals indicating severe hypo- or hypervolemia. Static markers are subject to numerous confounding factors, which limit their precision in the clinical setting. Even measuring baseline CO as a one-time static marker possesses only moderate predictive value to estimate volume status because the cardiac function curve characteristics differ among patients as well as within patients due to continuously changing pathophysiologic conditions. Moreover, any single value does not discriminate where a patient is located on the Frank-Starling curve; on the ascending limb or near the plateau of the curve. Although static markers often help assess a patient's hemodynamic status they do not predict if the patient will be fluid responsive or if vasopressors and/or positive inotropes should be initiated, limiting their value to tailor optimal treatment strategies in the individual patient (45).

Dynamic markers try to determine a patient's location along the curve by inducing a short-term change in preload (e.g., administration of a fluid bolus) and measuring the magnitude of response to the change in preload in real time. Therefore, dynamic markers assess at least two points on the curve to estimate a patient's fluid responsiveness. The magnitude of response is usually measured as a change in CO, SV, or their surrogates such as pulse pressure or other clinical parameters. Dynamic markers do not assess volume status, yet assess fluid responsiveness in order to decrease the incidence of fluid overload, as well as the risk of recurring hypotension.

In general, whether a parameter is considered static or dynamic depends if the parameter is measured at a single static point in time, or if an effect is measured in real time in response to a change in preload (e.g., fluid bolus). This means that most parameters, including clinical and point of care ultrasound (POCUS) can be considered both static and dynamic, depending whether a measurement is taken at a fixed time point or over a period of time in response to a preload challenge. For example, HR in isolation is a static marker, while a change in HR following a fluid bolus is a dynamic marker; the caudal vena cava (CVC) diameter in isolation is a static marker, while the CVC collapsibility index (CVC_{CI}), because of heart-lung interactions, is a dynamic marker (see below). Although many parameters can be assessed dynamically in response to a change in preload, many perform poorly because they are influenced by factors independent of preload. These markers are therefore more commonly employed as indicators of circulatory shock or used as static "alarm" markers (e.g., HR, urine output, CVP, etc.; see below). Moreover, many of these typical static markers are not sufficiently sensitive, or their measurement is not sufficiently precise to allow detection of small changes in preload, limiting their use as dynamic markers (26). In contrast, the ideal dynamic marker should be one that truly reflects fluid responsiveness, responding consistently and predictably to an induced change in preload for a specific volume status and not influenced by factors other than preload. To be considered a dynamic marker the parameter assessed should be sensitive and specific for fluid responsiveness, and the parameter should be measured with enough precision to allow for the accurate detection of small changes.

As mentioned, dynamic markers of fluid responsiveness are required to assess the capacity to improve tissue perfusion following an induced change in preload. Given fluid responsiveness aims to precisely titrate fluids, it is more commonly utilized after the initial resuscitation (fluid loading) phase of fluid therapy is complete. However, depending on the level of invasiveness and skill required to assess the dynamic parameter, the applications will vary. For example, the authors commonly assess parameters such as the left atrial to aortic (LA:Ao) ratio and caudal vena cava diameter (CVCd) to assess volume status and the CVC_{CI} to assess fluid responsiveness in the resuscitation phase of fluid therapy.

The preferred techniques used to assess fluid responsiveness may also differ depending on the clinical setting. Some techniques are less precise, yet less invasive, more rapid, and more easily applicable in a less controlled environment, making them perfectly suited for the triage or ER setting (**Figure 3**). More accurate techniques often require invasive lines, expensive equipment, and patient cooperation, and are typically reserved for a more controlled environment, such as an ICU setting. An overview of the different techniques is presented in the Eisenhower matrix in **Figure 3**. The following paragraphs will consider several parameters and their value as a static or a dynamic marker.

Traditional Static Markers

As mentioned above, many parameters can be measured in a static or dynamic fashion. However, the following section discusses clinical exam findings, MAP, shock index (SI), CVP, and lactate as primarily static markers in the clinical setting as evidence suggests they are not as accurate as some markers when assessed dynamically in response to a preload challenge.

Clinical Exam Findings

The purpose of the clinical examination in the patient with circulatory failure is to identify patients that are most likely to benefit from IV fluid therapy. The initial assessment of volume status begins with interpretation of clinical signs and symptoms including HR, pulse quality, mental status, jugular vein distention, urine production, skin turgor, temperature, capillary refill time (CRT), and the presence of peripheral edema (17, 25, 39). Although clinical examination findings have been studied and are integral to the assessment of perfusion status and the identification of shock in veterinary patients, studies assessing the accuracy of clinical parameters to specifically estimate volume status and/or volume responsiveness in dogs and cats are very limited (49–51). Research in anesthetized dogs suggests these parameters are not accurate at differentiating fluid responders from non-responders (16–19). A recent study in spontaneously breathing dogs with compromised hemodynamics or tissue hypoperfusion found CRT, presence of pale mucous membranes, HR, weak pulses and serum lactate concentrations all failed to differentiate fluid responders and non-responders (25). Studies in cats evaluating hemodynamic parameters to predict volume status and fluid response are lacking. Similar to canine studies, most human studies demonstrate clinical examination findings, particularly in isolation, fail to discriminate between

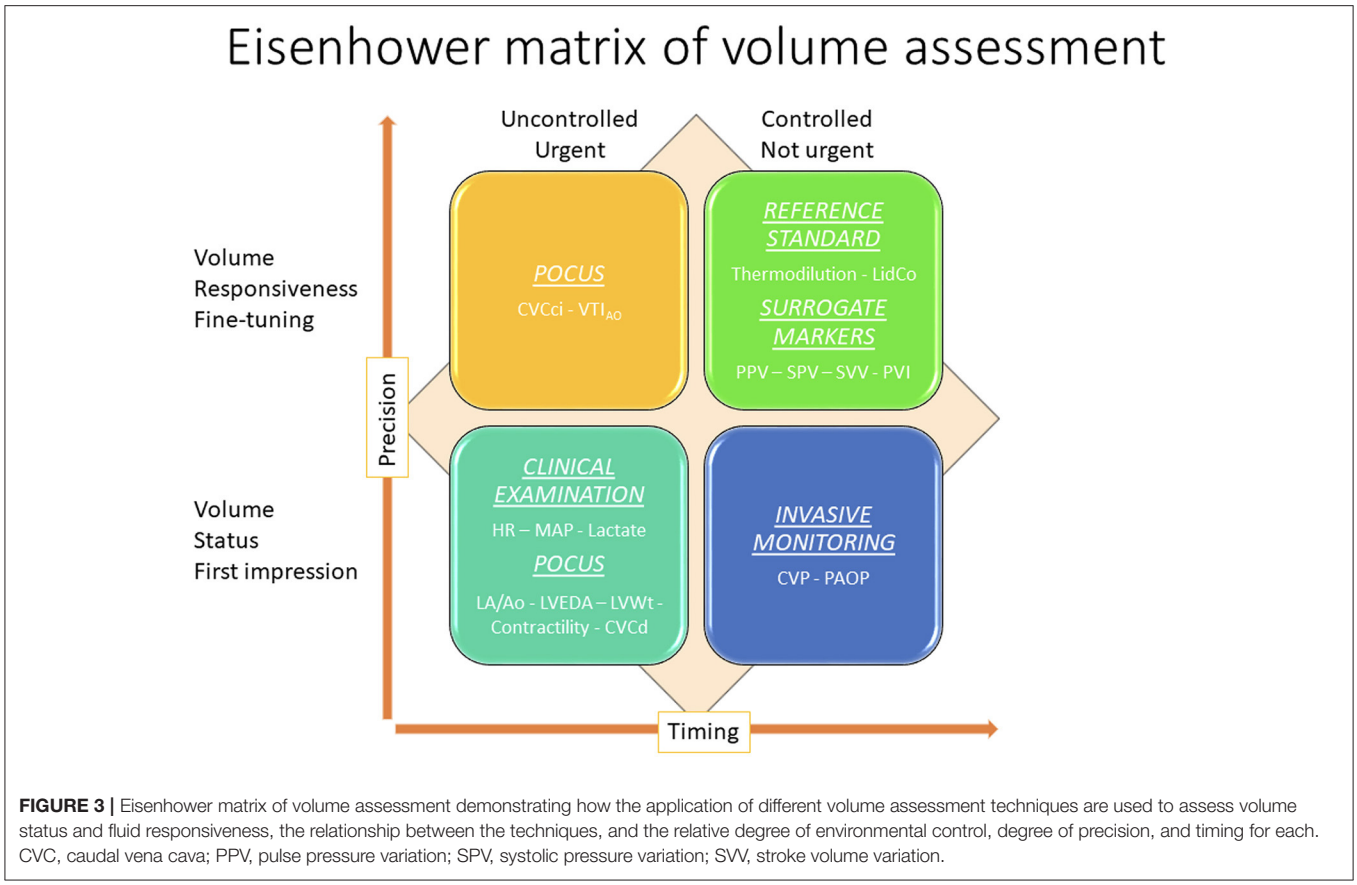

FIGURE 3 | Eisenhower matrix of volume assessment demonstrating how the application of different volume assessment techniques are used to assess volume status and fluid responsiveness, the relationship between the techniques, and the relative degree of environmental control, degree of precision, and timing for each. CVC, caudal vena cava; PPV, pulse pressure variation; SPV, systolic pressure variation; SVV, stroke volume variation.

hypovolemic and normovolemic individuals (36). However, there is some evidence in human ICU patients that using a combination of two or more physiological variables increases the sensitivity and specificity of a diagnosis of impending cardiovascular collapse (52). These examination methods should therefore be used together to identify patients suspected to be in shock and potentially trigger fluid administration (53). In addition, larger prospective clinical studies should be undertaken in veterinary medicine before recommendations regarding the accuracy of traditional static markers for the assessment of volume status and fluid responsiveness can be made in dogs and cats.

During circulatory dysfunction, the compensatory neurohumoral response redistributes blood flow to vital organs by reducing blood flow to non-vital structures such as the skin and mucous membranes. Subjective assessment of the temperature of the extremities (54–56), central to peripheral temperature difference (57), and CRT have been validated and shown to be relatively reproducible in human ICU patients to assess volume status (58). Unfortunately, clinical parameters such as CRT are operator dependent being affected by different duration of pressure, and both ambient and skin temperature (59). As mentioned above, a single study in spontaneously breathing dogs with hemodynamic compromise demonstrated CRT and the presence of pale mucous membranes could not differentiate fluid responders and non-responders (25). Therefore, although these parameters remain integral to the assessment of ECC patients to assess perfusion, they have poor sensitivity and specificity at predicting volume status (36). A change in these clinical parameters in isolation from other parameters should be interpreted cautiously as they may not accurately reflect the volume status of the patient.

Another marker that may be reflective of hypoperfusion is urinary output (36). Hypersthenuric oliguria suggests a hypovolemic state with poor renal perfusion. Oliguria is non-specific and may exist with any form of dehydration regardless of intravascular volume (36). Urine output is influenced by neurohormonal compensatory mechanisms that may preserve or even increase renal blood flow in the face of decreased blood volume and administration of IV fluids could alter renal perfusion by increasing venous congestion (60). Furthermore, there is mounting evidence that the presence of profound intrarenal microcirculatory abnormalities that are not related to global hypoperfusion in resuscitated human patients contribute to acute kidney injury associated with septic shock and major surgery (60). Assessing urine output as a dynamic marker of fluid responsiveness is hampered by the time required for the kidneys to respond to changes in vascular volume, as well as the fact that urine output is influenced by factors other than hemodynamic status. Accordingly, fluid administration does not imply restoration of normal diuresis will be achieved (61), and chasing an increase in urine output with fluid boluses is

considered a dangerous strategy by many authors as it can lead to fluid overload.

A specific HR that can be used to guide fluid resuscitation has not been well-studied in either the human or veterinary profession. Tachycardia is an important early sign of shock and is often considered a static marker indicative of hypovolemia (36). Although a dynamic decrease in HR following a fluid bolus suggests some degree of pre-existing hypovolemia, research in dogs suggests the ability of HR to predict fluid responsiveness is variable. A study in anesthetized dogs challenged with 10 ml/kg of synthetic colloid found the percentage decrease in HR was greater in fluid responders than non-responders (17). This is similar to a study in dogs undergoing abdominal surgery that showed a significant decrease in HR following a 10 ml/kg bolus of isotonic crystalloid over 10 min was only detected in fluid responders (18). However, a prospective study in 25 hospitalized dogs found HR decreased significantly in both fluid responders and non-responders following a 4 ml/kg mini isotonic crystalloid bolus, suggesting HR could not differentiate between the two groups (16). Several other studies in spontaneously breathing and anesthetized dogs also found changes in HR failed to differentiate fluid responders and non-responders (15, 19, 28, 32). These findings are similar to human ICU studies that also demonstrate the ability of a change in HR to predict fluid responsiveness is quite variable (62, 63). Unfortunately, assessment of HR as a dynamic marker of fluid responsiveness is limited by its poor specificity, being influenced by pain, anxiety, fever, anemia, and inflammation (36). Furthermore, mechanical ventilation and anesthesia are known to impede neural and humoral control of HR and the administration of positive or negative chronotropic medications further complicates interpretation of a change in HR for the prediction of fluid responsiveness (36). Although changes in HR alone should not be used to predict fluid responsiveness, in conjunction with other parameters, a decrease in HR following fluid administration suggests a positive response to fluid administration (36, 59). In other words a change in HR following a fluid bolus *a posteriori* suggests a positive response, but does not predict the effect of a subsequent fluid bolus.

Mean Arterial Pressure

Ensuring MAP remains above a target value is an established goal in maintaining adequate perfusion of vital organs, although it has not been studied extensively as a predictor of fluid responsiveness, particularly in veterinary medicine. Fluid loading is indicated if tachycardia and hypotension are attributed to fluid depletion (36). As an indicator of severity of hypovolemia both hypotension and tachycardia show good predictive value in human patients with hemorrhagic shock (64, 65), however, these are neither sensitive nor specific (36). Changes in MAP can be applied dynamically to assess fluid responsiveness, and an increase in MAP following a fluid bolus is reflective of an increase in CO and a positive hemodynamic response provided vascular tone is intact. A study in dogs presenting to the emergency room with non-cardiogenic hypotension demonstrated normalization of blood pressure following fluid therapy is associated with a favorable prognosis. However, the study was not designed to determine if blood pressure could predict volume status or response to fluid therapy (32). In contrast, when vascular tone is altered, a failure of MAP to increase following therapy does not imply the absence of a positive response. Inversely, MAP can remain unchanged despite an increase in CO because arterial blood pressure is tightly regulated (66). Most studies in anesthetized and spontaneously breathing dogs demonstrate MAP is unable to discriminate between fluid responders and non-responders even in the face of an increase in CO or SV (16–19, 25). The low predictive value of MAP is likely explained by the influence of underlying conditions on systemic vascular resistance (for instance, vasoplegia in sepsis), and individual variation in normotensive values. Furthermore, hypotension can be associated with non-hypovolemic shock states in which fluid resuscitation is contraindicated (e.g., congestive heart failure). Conversely, in some hypovolemic states compensatory mechanisms that increase vascular resistance may be sufficient to preserve MAP (53, 67). The International Consensus Conference on Hemodynamic Monitoring in 2006 found moderate-to-low evidence to implement target blood pressures in the management of shock in humans in the absence of relevant clinical studies (68).

Shock Index

Although HR and MAP individually are considered rather poor indices to guide fluid resuscitation, the identification of tachycardia coupled with hypotension should trigger the clinician to strongly consider fluid resuscitation in the absence of cardiac failure (36, 59). The combination of assessing HR and blood pressure in relation to each other has lead to development of the SI, which is the ratio of HR divided by systolic blood pressure (HR/SBP). The range of SI reported in dogs is quite variable and the precise cut off to identify shock is not well-defined (69–71), however a value of $\geq$0.9 has been associated with the presence of shock and increased mortality in dogs (69–71). Studies investigating the precision of SI to predict IV volume status and fluid responsiveness in veterinary patients are lacking. In people, the SI demonstrates a linear inverse relationship with CO and SV (72), and correlates with the extent of hypovolemia in severely injured patients, as reflected by higher rates of massive transfusion, morbidity, and mortality (73). Therefore, SI may prove to be a sensitive parameter for detection of hypovolemia and can be considered a trigger for fluid loading, although it must be considered in light of clinical findings as it lacks specificity, being increased in cardiogenic and obstructive shock. Moreover, as cats often present with bradycardia in response to shock, the SI requires investigation before it can be used in this species.

Central Venous Pressure and Pulmonary Artery Occlusion Pressure

Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are still two of the most commonly used hemodynamic monitoring tools in the assessment of volume status in human ICU's (26). Central venous pressure is a measure of pressure in the vena cava or right atrium and reflects RAP. PAOP reflects left atrial pressure and is measured by inserting a balloon-tipped, multi-lumen catheter (e.g., Swan-Ganz catheter) into a central vein, and advancing the catheter through the chambers of the right heart to the level of a branch of the

pulmonary artery. When the balloon is inflated, the branch of the pulmonary artery is occluded providing a pressure reading that is considered equivalent to the pressure of the left atrium. However, evidence in humans suggests CVP is a poor surrogate for RAP, cardiac filling pressure or preload changes (45). This is because the ventricular pressure-volume curve is not linear and the CVP is affected by alterations in cardiac, lung, and intrathoracic pressures (45). Both CVP and PAOP are invasive, relatively expensive, technically demanding to place, and have been associated with complications. However, given CVP was found to have clinical significance at very low and high values in human ICU patients, if a central line is placed for other reasons, extreme CVP values or consistent trends over time may still help identify states of severe hypo- and hypervolemia (26, 74). Although extreme values may help answer the clinical decision to start or stop fluid therapy, neither CVP nor PAOP can predict fluid responsiveness in people (26, 75). Similarly, evidence suggests CVP is not a good predictor of fluid responsiveness in dogs and performs poorly when compared to dynamic variables (17, 18). In summary, invasive lines should not be placed for the sole purpose of measuring CVP, but can be used when placed for other reasons. If used, CVP should be reserved for the detection of clinically relevant hypovolemia or hypervolemia, as opposed to determining optimal volume status. Given an increasing CVP during preload challenge in humans may have negative predictive power for fluid responsiveness it should not be used to predict or guide fluid resuscitation but may be used as a safety endpoint (26).

Blood Lactate

Blood lactate concentration is a downstream marker of tissue perfusion and a hallmark of shock, which is often used as a trigger to initiate and help guide fluid resuscitation (59, 72). However, lactate is non-specific and hyperlactatemia may be associated with any cause of decreased DO_2 or shock, regardless of volume status (45, 56). It may also be increased secondary to drug administration, decreased metabolism or elimination, or production by bacteria (76). Moreover, hyperlactatemia secondary to an anaerobic cellular metabolism in hypovolemic patients only occurs when a certain threshold of hypoperfusion has been reached; it is not sensitive at accurately identifying mild hypo- or even severe hypervolemia. Although lactate has been studied in veterinary medicine as a prognostic indicator in many disease states, research regarding the ability of lactate to discriminate between fluid responders and non-responders is lacking; a single study in spontaneously breathing dogs failed to demonstrate a difference in lactate between responders and non-responders (15). There is even less research regarding lactate and volume status in cats; it has been shown that hypotensive cats with normal lactate have a greater chance of survival than hypotensive cats with hyperlactatemia (39), however, lactate has not been studied as a hemodynamic marker of volume status or fluid response in cats. There is also recent evidence in the human literature that titrating fluid boluses based on lactate clearance in patients with septic shock may lead to volume overload with an increased risk of organ dysfunction and death (45). Therefore, similar to HR and MAP, lactate should be considered a good "alarm" signal, indicating a degree of urgency to initiate fluid resuscitation in patients suspected to be hypovolemic. Although it is a good marker of perfusion, in isolation lactate may not accurately reflect volume status or always predict fluid responsiveness.

Traditional Dynamic Markers

Fluid Bolus, Mini Bolus, Heart-Lung Interactions, and Passive Leg Raising

In order to dynamically assess any physiologic response to a preload challenge it is necessary to define and standardize what a preload challenge is. The preload challenge is designed to induce a change in preload that subsequently causes a measurable change in a physiologic parameter with minimal risk of causing fluid overload. Currently, a preload challenge may be defined as a traditional fluid bolus, mini fluid bolus, heart-lung interaction, or PLR. In veterinary medicine, consensus on what constitutes a fluid bolus is lacking but 10–20 ml/kg of isotonic fluid administered over 10–15 min is often used. In contrast a mini fluid bolus is typically 3–5 ml/kg of isotonic fluid administered over 1–5 min (14–16, 18, 20, 23, 24, 32–35, 77).

It is also possible to induce changes in preload without physically administering fluids through the principle of heart-lung interactions (45, 78). This can help predict patients that are fluid responsive, prior to fluid administration, and potentially reduce the amount of fluid given to non-responders. The relationship between intrathoracic pressure (ITP), VR and cardiac function forms the basis for understanding heart-lung interactions (**Figures 1B,C**) (78). It is based on the principle that changes in ITP during the respiratory cycle can be applied to form dynamic tests of fluid responsiveness. During spontaneous ventilation, ITP (the pressure within the pleural cavity) decreases during inspiration (becomes more negative) and increases during expiration. The inverse occurs with positive pressure ventilation (PPV), ITP increases with inspiration and decreases with expiration (29, 78). In a patient receiving PPV, during inspiration there is an increase in ITP and RAP. As VR relies on the difference between MCFP and RAP, it decreases during the inspiratory phase of PPV (**Figure 1C**) (29, 78). The decrease in VR during inspiration decreases right ventricular filling which subsequently decreases CO from the right ventricle. In addition, there is a direct effect of PPV on the heart during the inspiratory phase, which causes increased right ventricular afterload (79). The effects of this are seen on the left ventricle during expiration, due to pulmonary transit time. Pulmonary transit time means that the respiratory effects of ITP on the right side of the heart are mirrored by the left side of the heart but during the opposite phase of the respiratory cycle (79). Therefore, a decrease in left ventricular preload and decreased left ventricular output will be noted during expiration (30). By manipulating heart-lung interactions though manipulation of ventilator settings it is possible to increase preload and test fluid responsiveness of mechanically ventilated patients before administering any fluids. Alternatively, if positive pressure variables are held constant, serial changes in heart-lung interactions can be assessed in response to a fluid bolus or PLR maneuvers.

In human medicine, the administration of a "virtual fluid bolus" has been described through the application of PLR (80). PLR shifts the venous blood volume from the legs to the central circulation, acting as a reversible preload challenge. As the actual blood volume is unaltered, if the patient fails to respond appropriately or shows signs of volume overload, the "virtual bolus" can be reversed by simply returning the legs to a lower position. A major advantage of the PLR is the fact that it can be assessed using multiple different physiologic parameters, and therefore performed in both mechanically ventilated and spontaneously breathing patients, patients with cardiac arrhythmias, and those receiving low tidal volume ventilation (26). However, if pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV) and plethysmographic variability index (PVI), are used to assess the response of a PLR, then mechanical ventilation and general anesthesia will be required in most cases (see below). Although appealing, the PLR maneuver is more challenging in awake spontaneously breathing veterinary patients as a change in patient positioning may elicit an adrenergic/sympathic or "white coat response" in many companion animals. Adrenergic/sympathetic responses have been shown to confound changes induced by PLR maneuvers in people (81). The practicality of a PLR maneuver in veterinary medicine is limited to anesthetized swine, which coupled with the difficulty in being able to precisely and rapidly assess a response to a PLR maneuver, limits its application in the companion animal setting (31, 82).

In addition to standardizing and defining the preload challenge it is necessary to choose a physiologic variable that is easily measured and sufficiently sensitive to accurately detect even small changes in preload in order to minimize the risk of volume overload. In other words, for dynamic assessment of fluid responsiveness to be applicable, the assessed parameter must be sufficiently sensitive and precisely measured.

Cardiac Output

The reference standard to assess a patient's fluid responsiveness following a preload challenge is CO, which is an important part of tissue DO_2, along with the oxygen content of arterial blood. Cardiac output is also used to describe the response to increasing preload with the cardiac function curve (**Figure 2A**). Traditionally CO can be measured using thermodilution, LiDCo (lithium dilution CO), pulse contour analysis, and transthoracic impedance (22). However, these techniques are rarely used in the clinical setting and often reserved for research purposes as they tend to be invasive and require special equipment or training. Newer non-invasive devices based on electrical velocimetry (EV) methods have been experimentally introduced in dogs undergoing cardiovascular and cardiac surgery, and in client owned dogs with pulmonary hypertension and myxomatous mitral valve disease. They have shown promise in measuring CO, SVV, and fluid responsiveness although further research is required to determine the clinical applications of these methods in veterinary patients (83–86).

Pulse Pressure, Systolic Pressure, and Stroke Volume Variation

Surrogate markers for CO that have been used to dynamically assess fluid responsiveness include SVV, PPV, and SPV (76). These parameters are typically assessed in the anesthetized patient receiving mechanical ventilation and therefore necessitate a highly controlled environment with intensive monitoring. In the mechanically ventilated patient, a controlled change in respiratory pressure induces SVV, PPV and SPV due to the physiology of heart-lung interactions (**Figure 4**) (37, 76). The magnitude of the change varies with the patient's volume status and fluid responsiveness. A lower position on the Frank-Starling curve will induce larger variations during the respiratory cycle; positive fluid responders will demonstrate higher variations than non-responders (17, 21, 77, 87). In addition to the patient's volume status, the magnitude of change will vary depending on the tidal volume, positive inspiratory pressure, and positive end expiratory pressure chosen to induce a change in preload. Although many ventilator settings that influence the observed response can be controlled, others such as spontaneous respiratory effort, altered chest wall compliance, cardiac disorders (e.g., arrhythmias), right heart failure, and altered intra-abdominal pressures, are more difficult to control. Studies assessing dynamic markers in mechanically ventilated human and veterinary patients often fail to standardize the ventilator setting used to induce a change in preload or fail to agree on the magnitude of response used to define fluid responsiveness, making direct comparison of studies challenging (16, 17, 25, 35, 77, 78, 81, 87). Despite the lack of standardization, several studies have demonstrated the ability of dynamic variables to differentiate fluid responders from non-responders in anesthetized mechanically ventilated dogs. Regarding SVV, a study in healthy dogs that received fluid loading via continuous rate infusions of isotonic crystalloid at 90 ml/kg/h and synthetic colloid at 30 ml/kg/h found SVV of $\geq$11% to be the optimal threshold to predict fluid responsiveness (sensitivity 100%; specificity 100%) (88). This same study found the optimal threshold for PPV to predict fluid responsiveness was 7% (sensitivity 100%; specificity 100%). A study in client owned dogs undergoing abdominal surgical procedures demonstrated PPV could detect occult hypovolemia and predict cardiovascular response to a fluid bolus of 10 ml/kg isotonic crystalloids over 10 min; a PPV of $\geq$13% reliably predicted fluid responders in 82.8% of cases (18). Another study in healthy dogs exposed to 6 graded episodes of hemorrhage at 5 ml/kg, followed by 6 graded whole blood transfusions of 5 ml/kg showed moderate accuracy of PPV (sensitivity 71%, specificity 82%) to predict fluid response when a cutoff of $\geq$16% was used (21). Interestingly the SVV did not change in that study. A study using 10 ml/kg of synthetic colloid administered over 13 min demonstrated PPV is able to predict fluid responsiveness in healthy dogs when cut off values of 11% is used (sensitivity 79%, specificity 80%) (17). A study in client owned dogs undergoing orthopedic or oncologic procedures found PPV could predict fluid response following a 5 ml/kg isotonic crystalloid bolus administered over 15 min when the cut off of $\geq$15.6% was used (sensitivity 88%, specificity 100%) (19). A study in client owned dogs receiving 15 ml/kg of isotonic

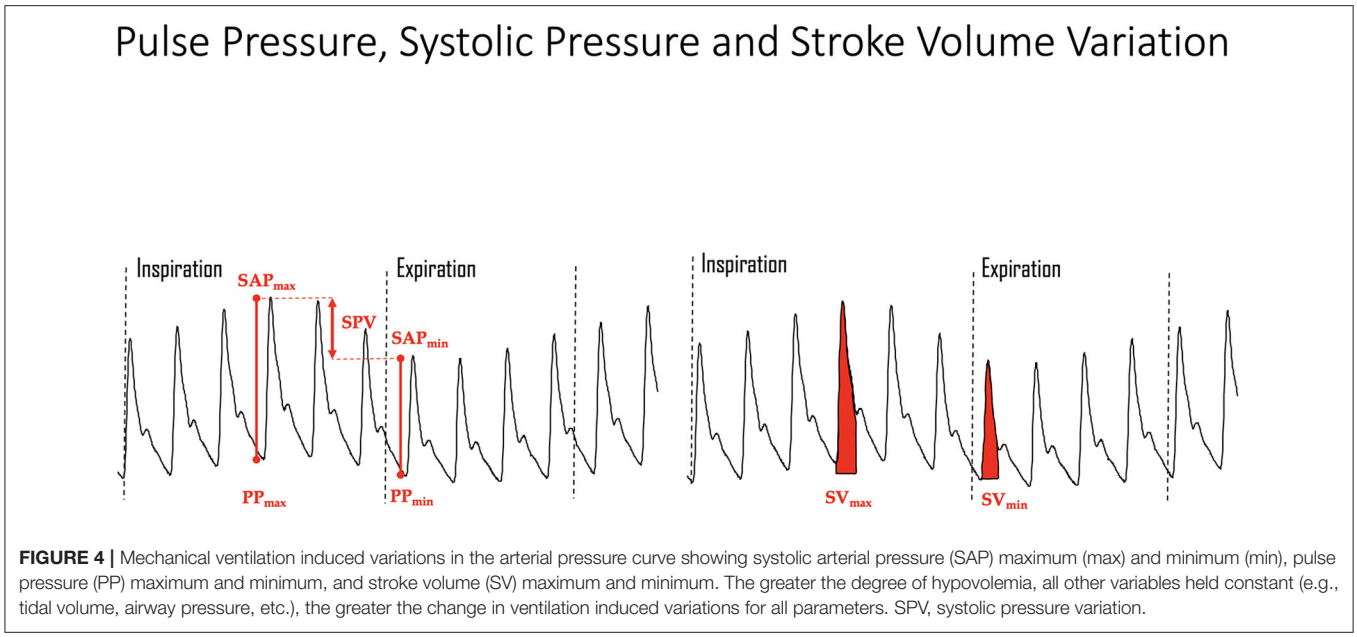

FIGURE 4 | Mechanical ventilation induced variations in the arterial pressure curve showing systolic arterial pressure (SAP) maximum (max) and minimum (min), pulse pressure (PP) maximum and minimum, and stroke volume (SV) maximum and minimum. The greater the degree of hypovolemia, all other variables held constant (e.g., tidal volume, airway pressure, etc.), the greater the change in ventilation induced variations for all parameters. SPV, systolic pressure variation.

TABLE 1 | Formula and reported threshold values to discern fluid responders from non-responders.

Parameter	Abbreviation	Formula	Human threshold	Canine threshold
Systolic pressure variation	ΔSP	$\Delta SP = SP_{max} - SP_{min}$	dDown > 5 mmHg (89)	dUp > 4 mmHg (35)
Pulse pressure variation	PPV	$\frac{(PP_{max}-PP_{min})\times 100}{(PP_{max}+PP_{min})/2}$	13.7% (90) 6.5–17% (91)	7 (71)–9.3% (17) 13% (18)–15.6% (92)
Stroke volume variation	SVV	$\frac{(SV_{max}-SV_{min})\times 100}{(SV_{max}+SV_{min})/2}$	10–22% (19)	11% (22)
Plethysmographic variability index	PVi	$\frac{(Pi_{max}-Pi_{min})\times 100}{Pi_{max}}$	14% (93) 9.5–19.0% (94)	11% (17)–13% (18)
Caudal vena cava collapsibility index	CVC ci	$\frac{CVC_{max}-CVC_{min}}{CVC_{max}}$	50% (95)*	30% (21)**

dDown, decrease in systolic pressure; dUp, increase in systolic pressure; max, maximal value obtained during a respiratory cycle; min, minimal value obtained during a respiratory cycle.
**Values higher than 50% are strongly associated with hypovolemia rather than indicative of fluid responsiveness.*
***Mean value in healthy normovolemic dogs.*

crystalloids over 15 min found PPV with a cut off of 15% was ideal to distinguish fluid responders and non-responders (sensitivity 50%, specificity 96%) (24). A 1 ml/kg isotonic crystalloid bolus administered to healthy dogs demonstrated SPV to be reliable predictor of fluid response when a cutoff of >6.7% was used to identify responders (sensitivity, 77.8%, specificity, 93.3%) (23). A study on healthy client owned dogs found the optimal threshold for SPV to detect fluid responders was 4.5% when a 3 ml/kg mini fluid bolus was administered over 1 min (sensitivity of 90%, specificity of 87%) (35). However, results of this study are difficult to compare with others as the reference standard used to define fluid response was a 10% decrease in HR and/or increase in MAP in response to the mini fluid challenge, which as discussed, are not reliable indicators of fluid responsiveness. All other studies used echographic derived calculations of CO and/or SV with increases of >10–15% as the reference standard to define a fluid response, except for three studies that used transpulmonary thermal dilution CO (21, 22, 88). Overall, these studies support the use of dynamic variables to predict fluid response in dogs, however, cut off variables differed significantly between studies, which is likely explained by the lack of standardization regarding the volume, type and rate of the fluid administered as well as ventilator settings used. If one combines the results from veterinary studies, fluid-responsiveness can generally be defined as a variation of ≥10–15% in the dynamic parameter measured. Moreover, the greater the variation, provided other variables remain constant, the more likely the patient will benefit from additional fluid boluses (see the gray-zone approach). Research in cats regarding the ability of SVV, PPV, SPV to detect fluid responders and non-responders is lacking.

Plethysmographic Variability Index

Plethysmographic variability index (PVI) is an automatic measure of the dynamic change in perfusion index (PI), as determined by a pulse oximeter, occurring during a complete respiratory cycle. PI demonstrates the pulse strength at the

sensor site and represents a relative value of tissue perfusion and blood flow at the site of measurement, which can change based on the patient's clinical status. The pulse oximeter derived pulsatile signal is indexed against the non-pulsatile infrared signal and expressed as a percentage reflecting the amplitude of the pulse oximeter waveform. More precisely, the measurement of PVI involves mathematical calculations using PI which are automatically performed by the internal software installed in the pulse oximeter. The PVI is calculated as [(PImax – PImin)/PImax] × 100 (37) (see **Table 1**). It is considered a non-invasive alternative to PPV for assessment of fluid responsiveness, with higher variability in the plethsmographic waveform being associated with preload dependence and fluid responders (14, 18, 21, 87, 96). A study investigating PVI in dogs undergoing abdominal surgery demonstrated a positive correlation between PPV and PVI, although a threshold for PVI to identify fluid responders was not established (18). Studies in healthy dogs subject to hemorrhage and transfusion of removed blood, as well as synthetic colloids demonstrated PVI had moderate to good ability to predict a positive fluid response with cut off values of 9.3–12% (sensitivity 78–86%, specificity 70–72%) (21, 22). Because PVI is dependent on pulse oximetry readings, it is subject to the same limitations as pulse oximetry; skin pigmentation, ambient light, motion artifact, vascular tone and peripheral perfusion are confounding factors that may prevent accurate values from being obtained (82, 87, 97). Although it does not require an invasive line, given the incidence of confounding factors likely to be encountered in hypovolemic patients it remains to be determined whether PVI is clinically applicable in veterinary patients with circulatory shock. PVI is also dependent on heart lung interactions and therefore subject to the same limitations as PPV, SVI, and SVV. There are also species differences that can affect pulse oximetry readings, which may subsequently influence PVI calculations in veterinary patients if human monitors are used (97).

Point of Care Ultrasound

Similar to several parameters already discussed, assessment of point of care ultrasound (POCUS) parameters can be assessed in a static fashion to estimate volume status or applied dynamically to assess fluid responsiveness. POCUS for volume status and fluid responsiveness includes both cardiac and vascular components.

Cardiac POCUS

Cardiac POCUS, also referred to as abbreviated echocardiography, is commonplace in many human ICU settings, predominantly because of its rapid, non-invasive, real time ability to assess patient volume status (98). Clinical research demonstrates cardiac POCUS applied to human patients with indeterminate volume status results in a change in therapeutic management and improved medical decision making (99). Estimation of volume status predominantly focuses on the subjective assessment of cardiac contractility, ventricular lumen size, ventricular wall thickness, and atrial lumen size, all of which require minimal training to learn (98). Similar to humans, dogs and cats with clinical signs of hypovolemia may develop smaller left ventricular and left atrial lumen sizes, and thicker left ventricular walls, referred to as pseudohypertrophy (100–102) (**Figures 5A,B**). Studies in cats, dogs and people suggest these changes are proportional to the severity of hypovolemia and reversible following successful volume replacement (98–103). In human patients with normal clinical parameters, cardiac POCUS may detect smaller left ventricular cavity and atrial size, indicating volume status is suboptimal (48, 52). Preliminary research in dogs suggests cardiac POCUS may have a higher sensitivity for detection of changes in volume status when compared to clinical parameters (100), although the number of canine studies was small and further research is recommended to corroborate these findings. In an experimental study in cats, volume depletion to the level of a 7–10% body weight reduction resulted in the cardiac POCUS findings of decreased ventricular and atrial lumen size, while left atrial and ventricular lumen size increased following volume administration (101).

Left atrial size is probably the easiest clinical cardiac POCUS parameter to assess for volume status estimation in dogs and cats (**Figures 6A–C**). It is non-invasive, inexpensive, and repeatable, requiring minimal training (104). Either short or long axis right parasternal views can be used to assess left atrial size. In both dogs and cats the normal LA:Ao ratio varies from 1 to 1.5 when measured via the right parasternal short axis window (105, 106). Alternatively, subjective estimation of the number of times the (area of the) aorta can be fit within the left atrial lumen has also been evaluated in cats. In a healthy cat, when looking at the short axis view of the left atrium, if the area of the left atrium is more than 2.5 times the area of the aorta, the left atrium should be considered enlarged (107). The upper reference range for the left atrial width in the long axis view of cats is 16 mm (or up to 18.5 mm in large breed cats such as Norwegian Forest cats or Maine Coons) (108). Although a decrease in left atrial lumen size in a patient with clinical signs of hypovolemia is strongly suggestive of a hypovolemic state, obstructive disease cannot be ruled out. For example, studies in healthy dogs with experimentally induced pericardial effusion developed echographic signs of pseudohypertrophy, including a small left atrium (109). Conversely, an increased left atrial lumen size may occur secondary to hypervolemia, congestive heart disease, or dilated cardiomyopathy.

In addition to changes in lumen size, the ventricular wall thickness should be considered relative to the dimensions of the left ventricular lumen in dogs and cats (100, 101). Although not specific, both thin or "stretched" ventricular walls and thick ventricular walls in diastole can be indicative of hypervolemia and hypovolemia, respectively. However, given thin walls may also be a consequence of dilated cardiomyopathy or regional lesions (e.g., myocardial infarction) and myocarditis, and ventricular hypertrophy can lead to thick ventricular walls, interpretation of findings in light of the entire clinical picture is imperative when assessing volume status.

Subjective and objective assessment of contractility of the left ventricle can also be assessed in relation to volume status, with increased contractility being seen in response to compensatory shock states and as an adaptive response to ventricular filling

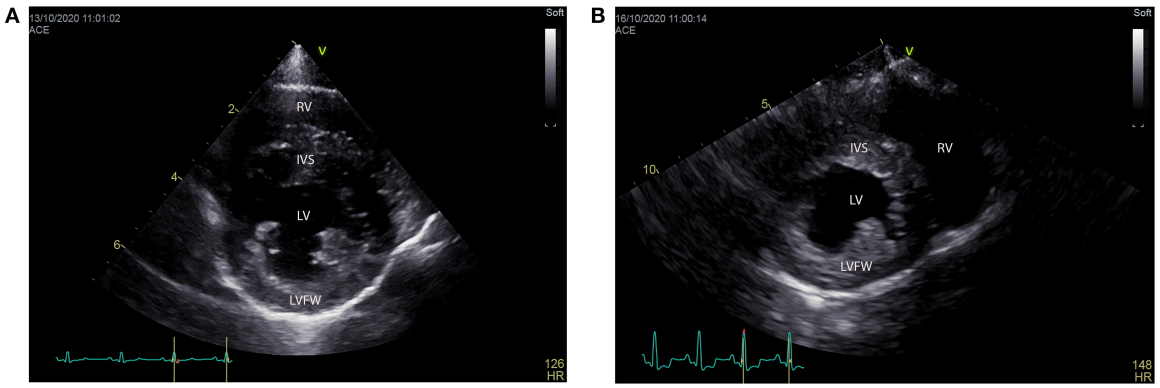

FIGURE 5 | (A,B) Right parasternal short axis views from a normal (left) and hypovolemic (right) dog. Note how the left ventricular lumen (LV) appears smaller than the lumen of the normovolemic dog and both the intraventricular septum (IVS) and left ventricular free wall (LVFW) appear thicker. RV, right ventricle.

(110, 111). However, confounding factors such as hypertrophic cardiomyopathy, or even stress or pain via their effect on sympathetic tone can result in increased contractility decreasing the specificity of cardiac POCUS contractility assessment to detect hypovolemic states (110, 111). Although cardiac POCUS appears promising in veterinary medicine for assessment of volume status and can act as a trigger to start or discontinue fluid resuscitation, clinical studies validating its use and accuracy are lacking.

Measurement of left ventricular end-diastolic area (LVEDA) has been used for assessment of volume status in the human critical care setting due to its simplicity of measurement (112). It is measured at the level of the papillary muscles in the parasternal short axis window at end-diastole by tracing the endocardial border (113). A small LVEDA (<10 cm^2 in humans) suggests significant hypovolemia, while an enlarged LVEDA (>20 cm^2 in humans) suggests volume overload (114). Obliteration of the left ventricular cavity would be seen in severe hypovolemia (115). It should be kept in mind that LVEDA is considered a static marker and prone to the same limitation as other static markers of volume status. Concentric left ventricular hypertrophy and constrictive pericarditis may also cause a small LVEDA independent of volume status (112, 116). Furthermore, specific cut offs for LVEDA have not been established (112) and a recent meta-analysis demonstrated failure of the LVEDA to predict volume responsiveness in mechanically ventilated human patients (117).

At a more advanced level CO can be directly calculated based on the cross-sectional area of the descending aorta and the left ventricular outflow tract volume time integral (LVOT VTI), which has been used to predict fluid responsiveness in both humans and dogs (15, 116). The product of these factors is equal to the column of blood that is ejected from the heart during each contraction. Similar to previously discussed parameters, heart-lung interactions will induce a change in LVOT VTI. Alternatively, changes in LVOT VTI can be measured dynamically before and after a mini fluid bolus or PLR in humans, similar to other traditionally measured dynamic markers. A recent study demonstrated the accurate assessment of fluid responsiveness in conscious dogs using the LVOT VTI (15). Unfortunately, sonographic assessment of LVOT VTI requires a much higher skill level compared to other POCUS measurements. A small error in the calculation of the aortic surface, as well as a slightly altered angle when assessing the LVOT VTI by Doppler ultrasound can induce changes in measurements that are greater than the expected change induced by a mini-bolus or heart-lung interactions.

Caudal Vena Cava Diameter and Collapsibility Index

Inferior vena cava diameter (IVC_d) has become well-established in many human ECC settings as a means of assessing volume status (118). In companion animals, caudal vena cava (CVC) assessment has been described at the suprailiac (kidney), the right intercostal (transhepatic) and the subxiphoid (diaphragmatic) level (119). Research suggests all three sites can easily be assessed in dogs, although inter-rater variability at the subxiphoid view is higher than the suprailiac or right intercostal approaches (119). In contrast to human medicine where the IVC is commonly used in the ECC setting (98), recent surveys demonstrate many veterinarians lack confidence and require further training to feel comfortable evaluating the caudal vena cava (CVC) (120, 121). Assessing the CVC may also be challenging in patients with abdominal discomfort.

Studies in human medicine demonstrate that a decreased, or small/flat, IVC diameter (IVC_d) correlates with hypovolemia and poor IVC dilation following fluid resuscitation suggests inadequate intravascular volume, independent of arterial blood pressure. Similar to humans, CVC diameter (CVC_d) has been shown to correlate with volume status and CVP in dogs (122). An experimental model of clinically undetectable hypovolemia in dogs created through blood donation (roughly 8% blood volume) demonstrated mixed results ranging from no significant change to a mild yet significant decrease in the CVC_d (123–125). Inversely, in dogs with chronic degenerative mitral valve disease (DMVD), increasing American College of Veterinary Internal Medicine (ACVIM) disease stage is associated with

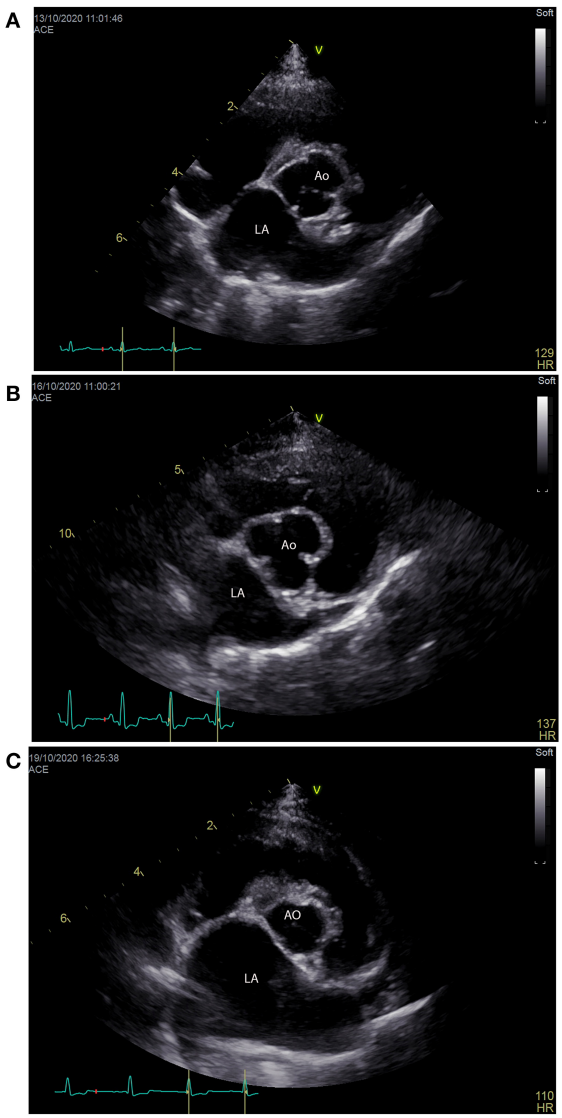

FIGURE 6 | (A–C) Right parasternal short axis views showing the left atrial (LA) size compared to the aorta (Ao) size from 3 different dogs that were normovolemic **(A)**, hypovolemic **(B)** and hypervolemic **(C)**. Note the size (width) of the left atrium is only slightly larger than the aorta in a normovolemic patient **(A)**, equal to slightly smaller than the aorta in a hypovolemic patient **(B)** and significantly larger than the left atrium in a patient that is hypervolemic **(C)**.

higher CVC_d secondary to fluid retention and hypervolemia (126) (**Figures 7A,B**).

In addition to the correlation of the CVC_d with blood volume, the thin elastic nature of the CVC also makes it a responsive and dynamic vessel. The size and geometry fluctuate in response to relative and absolute intravascular volume changes depending on the cardiac and respiratory cycle (see **Supplementary Videos 1–3**). Breathing changes intrapleural pressures, generating heart-lung interactions, thereby influencing the intravascular volume within the thorax and abdomen. This change in size of the CVC between inspiration and expiration, referred to as CVC collapsibility, is calculated as a collapsibility index (CVC_{CI}). The CVC_{CI} expresses the percentage change in the diameter of the CVC during the respiratory cycle based on the following formula: $CVC_{CI} = (CVC_d \text{ max} - CVC_d \text{ min})/CVC_d \text{ max}$ (see **Table 1**).

The IVC_{CI} has shown promise in human medicine to predict fluid responsiveness (127). A "fat" IVC, subjectively defined as wide IVC with an $IVC_{CI} < 50\%$ is associated with a high CVP secondary to hypervolemia, congestive heart disease or cardiac tamponade. Inversely, a flat IVC, defined as a narrow IVC with an $IVC_{CI} > 50\%$ is correlated with a low CVP and is indicative of hypovolemia. Mean IVC_{CI} values reported in healthy adult humans are $47.3 \pm 8.9\%$ (128). An advantage of the IVC_{CI} in humans is the fact it can be assessed in patients undergoing positive pressure ventilation, and in critically ill spontaneously breathing patients (129, 130). Although the threshold to distinguish fluid responders from non-responders in spontaneously breathing patients varies between studies (see gray-zone approach), an $IVC_{CI} \geq 48\%$, predicts fluid responsiveness with a sensitivity of 84% and a specificity of 90% (129). Despite these promising findings, IVC assessment is influenced by factors such as cardiac function, respiratory effort, intra-abdominal pressure, and pressure artifact (131).

There are limited veterinary studies examining the use of CVC_{CI} in dogs or cats to assess fluid responsiveness. Blood donation in dogs appears to be associated with an increased CVC_{CI} (124). More advanced ACVIM stage of DMVD in dogs also is associated with a decreased CVC_{CI} (126). A canine study indicated CVC_{CI} can predict fluid responsiveness under controlled circumstances in anesthetized and mechanically ventilated dogs (23). Although these findings suggest the CVC_{CI} is a promising marker of fluid responsiveness in companion animals, further research is required before guidelines on its application can be recommended. A very small clinical study ($n = 27$) in spontaneously breathing dogs with compromised hemodynamics or tissue hypoperfusion suggested that CVC_{CI} can accurately predict fluid responsiveness, although the authors also concluded research is necessary to extrapolate their results to larger populations of hospitalized dogs (25).

Lung Ultrasound and Other POCUS Findings Suggestive of Volume Overload

Despite significant advances in the understanding of the physiology behind fluid therapy, hemodynamically unstable human and veterinary ECC patients often receive IV fluids without defining clear end points of fluid resuscitation or start points for fluid removal (132). Failure to identify end points of fluid resuscitation may lead to fluid overload and increased EVLW (45, 132–134). Evidence suggests that increased EVLW can be detected with lung ultrasound (LUS) through the identification of increased B lines: comparison of a reference standard for detection of EVLW and LUS for detection of increased B lines shows there is a direct correlation between the two (135–137), and evidence in humans shows the sensitivity and specificity of LUS to identify pulmonary edema (defined as increased B lines) is as high as 97 and 95%, respectively.

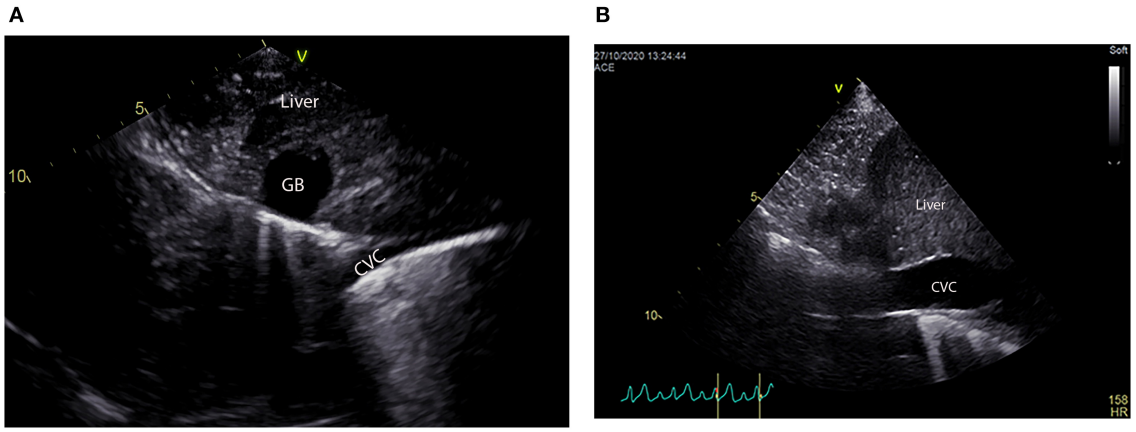

FIGURE 7 | (A, B) Long axis views of the caudal vena cava (CVC) as it crosses the diaphragm assessed at the subxiphoid site of 2 dogs that were hypovolemic **(A)** and hypervolemic **(B)**. Note the CVC is very narrow or "flat" in the hypovolemic dog and quite wide or "fat" in the hypervolemic dog. There is also a suspicion of free abdominal fluid between the liver lobes in the hypervolemic dog, although free fluid cannot be differentiated from artifact in this single still image. Free abdominal fluid would not be unexpected in dogs with hypervolemia and a more thorough point of care ultrasound evaluation would be recommended to further assess this finding.

B lines are lung surface artifacts that result from a proportional increase of fluid in the interstitium and/or alveoli, which creates a high fluid-air impedance gradient between the fluid and air within the lung (138). These B lines appear sonographically as hyperechoic (white) vertical narrow (individual) to broad (coalescing) bands that extend vertically from the lung surface and move synchronously with lung sliding (**Figure 8**) (139, 140). In healthy veterinary patients it is possible to detect B lines in up to 31% of patients, however it is more common to find only a single isolated B line at 1 location on either hemithorax, or two B lines at a single location when scanning the lung surfaces of dogs and cats (141–144). Although 3 B lines at a single location has been described in healthy cats and dogs, this number of B lines in a single sonographic window is rare and should not occur at multiple lung locations over the same hemithorax (142, 143). The appearance of >3 B lines in a single lung ultrasound window, or a serially increasing number of B lines relative to base line is suggestive of "wet lungs" (142, 143, 145). However, as increased B lines are not specific and may result from numerous alveolar interstitial pathologies (e.g., fluid overload, left sided congestive heart failure, pulmonary contusions, aspiration pneumonia, acute respiratory distress syndrome, fibrosis, neoplasia, etc.) it is important to identify the underlying cause to direct appropriate diagnostics and therapy (146–150).

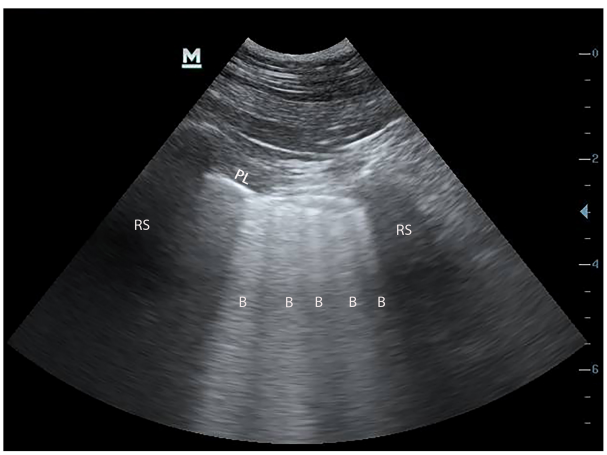

FIGURE 8 | Still ultrasound image obtained during pleura and lung ultrasound (PLUS) in a dog with "wet lungs." The presence of >3 B lines is considered "wet lung" and indicates increased extravascular lung water. Although there are multiple causes of "wet lung," fluid overload should be suspected in a patient that has received fluid therapy fluid, particularly if the patient progresses from dry to wet lung on serial PLUS evaluation.

The correlation between increased B lines and EVLW has led to the development of the fluid administration limited by lung sonography (FALLS) protocol in human ICU settings to help physicians detect a safety threshold for fluid resuscitation in patients presenting in shock (151). The FALLS protocol is based on the principle that LUS can accurately detect increased B lines ("wet lung") in patients with increased EVLW, which can be used to help guide management of patients presenting with unexplained circulatory shock. Based on the FALLS protocol patients with uncomplicated hypovolemic shock that have not yet received fluid boluses will have an absence to very few B lines, or "dry lungs," throughout all sonographic lung fields. Tailored fluid therapy in these patients should correct hypovolemia without leading to an increase in B line numbers or "wet lungs." The FALLS protocol will also detect most patients that present with cardiogenic shock and left-sided congestive heart failure as these patients typically are in a state of volume overload at presentation and will likely have "wet lungs" on initial LUS evaluation. Successful therapy of left sided congestive heart failure should result in a serial decrease in the number of B lines detected on LUS (145,

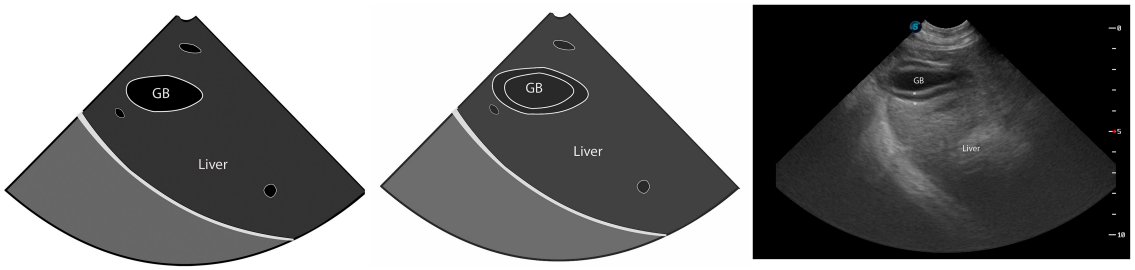

FIGURE 9 | (A–C) Schematic images of a normal (left) gall bladder, gall bladder wall edema also referred to the halo sign (middle), and still ultrasound image of the halo sign (right). With gall bladder wall edema there is a thickening of the gall bladder wall but also a "striated" appearance that arises when anechoic fluid (black) separates the mucosal and serosal surfaces of the gall bladder wall (white). The serosal and mucosal surfaces of the gall bladder wall are indicated by an asterix in the still image. GB, gall bladder.

152). Finally, patients with sepsis and distributive shock are more likely to develop "wet lungs" during fluid loading, despite continuing signs of circulatory failure. If a patient progresses from "dry" to "wet lungs" at any point in time further patient evaluation and re-assessment of the fluid therapy plan is indicated.

Additional POCUS findings that may be identified in patients developing volume overload secondary to excessive fluid administration include fluid accumulation in body cavities and development of gall bladder wall edema, often referred to as a gall bladder "halo sign" (**Figure 9**) (122). Although the development of a gall bladder halo sign is non-specific and commonly associated with anaphylaxis (153), the appearance of a halo sign during fluid loading can be suggestive of hypervolemia. If the halo sign occurs secondary to hypervolemia with increased right atrial pressure, it is often associated with other sonographic findings suggestive of volume overload, such as an enlarged CVC (see above) and/or the appearance of pleural effusion and/or free abdominal fluid (122).

In summary, POCUS findings suggestive of volume overload include enlarged left atrial and ventricular lumen size, thinning of the ventricular walls, a distended CVC with a decreased CVC_{CI}, increased number of B lines, gall bladder wall edema and body cavity fluid accumulation. As these findings are not specific, it is important to interpret POCUS findings in light of the entire clinical picture.

CONCLUSIONS

Optimizing individual fluid therapy is complex with very little veterinary evidence available to guide clinical decision-making. However, a greater knowledge and understanding of the differences between volume status and fluid responsiveness, and the factors influencing both allow the clinician to interpret clinical findings with greater confidence. The decisions regarding estimation of fluid volume and fluid responsiveness vary depending on the clinical scenario and how well the patient's environment can be controlled. POCUS provides rapid real time patient assessment that can guide volume status and fluid responsiveness regardless of the setting. The clinician should however consider a gray-zone approach in answering the question of volume status and fluid responsiveness to minimize clinically relevant hypo- or hypervolemic states and ensure optimal fluid management in critical care patients. Within the gray-zone approach more precise titration of fluids becomes paramount and fluid responsiveness should be assessed through techniques that minimize the risk of volume overload; small IV bolus administration, and/or assessment of parameters that respond to heart-lung interactions in the absence of administering fluids.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.630643/full#supplementary-material

Supplementary Video 1 | Caudal vena cava (CVC) changes in a dog with hypovolemia. Note the change in diameter of the CVC between inspiration and expiration (the CVC collapsibility index) is easily visible and subjectively changes by about 90%. Smaller pulsatile fluctuations in the CVC as a results of the cardiac cycle are also visible. The degree of change in the CVC diameter visible during the cardiac and respiratory cycles is consistent with hypovolemia and a patient that is likely fluid responsive.

Supplementary Video 2 | Caudal vena cava (CVC) changes in a dog with increased right atrial pressures. Note there is minimal change in diameter of the CVC between inspiration and expiration (the CVC collapsibility index), and the smaller pulsatile cardiac fluctuations in the CVC are absent. The lack of visible change in the CVC diameter during the cardiac and respiratory cycles in this dog is consistent with increased right atrial pressures (e.g., iatrogenic fluid overload, pericardial effusion, right sided heart failure etc.). Further work up is recommended to determine the cause.

Supplementary Video 3 | Caudal vena cava (CVC) changes in a cat that accidently received a blood transfusion over 10 min. Note there is minimal change in diameter of the CVC between inspiration and expiration (the CVC collapsibility index), and the smaller pulsatile fluctuations in the CVC as a results of the cardiac

cycle are absent. The lack of visible change in the CVC diameter during the cardiac and respiratory cycles is consistent with increased right atrial pressures, and in this case secondary to volume overload from rapid blood transfusion therapy. Pleural effusion is also visible which was not present when the cat presented, which further supports volume overload. The cat was successfully treated for iatrogenic volume overload with furosemide.

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Fluids of the Future

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Fluids are a vital tool in the armament of acute care clinicians in both civilian and military resuscitation. We now better understand complications from inappropriate resuscitation with currently available fluids; however, fluid resuscitation undeniably remains a life-saving intervention. Military research has driven the most significant advances in the field of fluid resuscitation and is currently leading the search for the fluids of the future. The veterinary community, much like our civilian human counterparts, should expect the fluid of the future to be the fruit of military research. The fluids of the future not only are expected to improve patient outcomes but also be field expedient. Those fluids should be compatible with military environments or natural disaster environments. For decades, military personnel and disaster responders have faced the peculiar demands of austere environments, prolonged field care, and delayed evacuation. Large scale natural disasters present field limitations often similar to those encountered in the battlefield. The fluids of the future should, therefore, have a long shelf-life, a small footprint, and be resistant to large temperature swings, for instance. Traumatic brain injury and hemorrhagic shock are the leading causes of preventable death for military casualties and a significant burden in civilian populations. The military and civilian health systems are focusing efforts on field-expedient fluids that will be specifically relevant for the management of those conditions. Fluids are expected to be compatible with blood products, increase oxygen-carrying capabilities, promote hemostasis, and be easy to administer in the prehospital setting, to match the broad spectrum of current acute care challenges, such as sepsis and severe systemic inflammation. This article will review historical military and civilian contributions to current resuscitation strategies, describe the expectations for the fluids of the future, and describe select ongoing research efforts with a review of current animal data.

Keywords: blood product development, hemorrhage, innovation, resuscitation, sepsis, shock, traumatic brain injury

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THE DRIVE FOR THE FLUIDS OF THE FUTURE

Military Research and Needs

Military research has driven much of the resuscitation advances over the years. Large scale conflicts and field-specific demands have outlined the need to address common conditions. Hemorrhagic shock, traumatic brain injury, burns, and sepsis are responsible for the vast majority of combat casualties from the most recent conflicts in the Middle East (1–3). Hemorrhage remains by far

the leading cause of preventable deaths (1). Those observations lead the military trauma community to develop field-expedient solutions relevant to operative constraints.

Civilian Resuscitation

While resuscitation differs drastically between a warzone and a civilian setting, there is still a need for novel resuscitation fluids in non-combat scenarios. Patient care at the point-of-injury and during transport to definitive care can also be challenging during non-military operations. This is illustrated by massive casualties scenarios where blood supplies and resuscitation teams are rapidly exhausted. Resuscitation resources may be overwhelmed and exhausted following natural (hurricanes, flooding, etc.), or human-made disasters (terrorist attacks). Resuscitation in underserved areas, such as rural communities or Native American reservations, presents similar challenges. Care-providers practicing in those environments will likely benefit from field-expedient novel fluids. Most deaths occur within the first 6 h following trauma (4), which emphasizes the importance of adequate resuscitation tools near the point-of-injury.

Veterinary Resuscitation

Military working dogs are exposed to significant hazards during deployment and suffer similar injuries as their human counterparts. Hemorrhagic shock and sepsis are also concerning in those patients. There is limited research explicitly pertaining to canine resuscitation in austere environments and prolonged field care scenarios.

Civilian veterinary populations will also benefit from advances toward fluids of the future. Law enforcement and search and rescue dogs may present similar injury patterns as military working dogs (5). They often operate in austere environments with limited resources and may suffer similar injuries (gun, stab wounds, burns, impalement, etc.). Aside from potential medical benefits over current products, fluids of the future are also likely to be used in smaller clinics that cannot carry products with demanding storage requirements or a short shelf life.

THE IDEAL FLUID

Shock is defined by the American College of Surgeons as the inadequate perfusion of tissue, such that the oxygen and blood volume delivery fail to meet the cellular metabolic and oxygen consumption needs. This definition does not however account for cytopathic shock, whereby cells may not be able to produce ATP despite normal oxygen delivery (6–8). Therefore, the treatment of shock focuses on restoring tissue oxygen delivery by improving blood volume and flow in both the macro and microcirculation. Sustaining arterial content of oxygen is a cornerstone of resuscitation as well. However, despite the normalization of markers of tissue oxygen delivery (blood pressure, hemoglobin concentration, arterial partial pressure in oxygen, etc.), patients may suffer ongoing organ injury due to microcirculation and mitochondrial disorders. The ideal fluids should provide a solution to the various components of the physiopathology of shock. While the quest for the ideal fluid is still ongoing, its characteristic can be outlined in **Table 1**.

NOVEL CRYSTALLOIDS

Crystalloids, both hyper- and isotonic, have been extensively studied for the management of various types of fluid-responsive shocks. Advances in knowledge have also underlined their limitations, such as hemodilution, blood acidification, hypothermia, coagulopathies, etc. (9). Those side effects serve as a canvas for research and development efforts.

Recently a crystalloid that supports nitric oxide synthesis (by containing nitrate and nitrite) and free-radical scavenging (by containing magnesium and transition metals) was similar to whole blood at improving hemodynamic markers of hypoperfusion (mean arterial pressure, serum lactate, central venous oxygen saturation) in pigs subjected to hemorrhagic shock (10). This product showed similar histological markers of tissue and glycocalyx injury compared to whole blood. Such effort seeks to address microcirculatory dysfunction observed during states of shock, while utilizing a non-hemoglobin-based resuscitation tool.

Another approach has been to add polymers of polyethylene glycol (PEG) to exert osmotic and hydrophilic actions in the microcirculation. Much remains to be done regarding the coagulation effects of the product (11); pigs subjected to hemorrhagic shock and resuscitated with the investigational product had reduced maximal amplitudes when compared to control animals. The solution still showed promising results in pre-clinical studies comparing it to whole blood or starches

TABLE 1 | Desirable properties of an ideal resuscitation fluid.

Example of characteristics for the ideal resuscitation fluid
No storage lesion for prolonged periods at ambient temperatures up to 130°F (54°C)
Ready or easily prepared for use
Universally compatible
Support oxygen-carrying capacity
Mitigates or negates post-shock, post-resuscitation syndromes
Compatible with blood products
No impairment of coagulation capability
Minimal or mitigating effect on edema
Improves microcirculation
Enhance cellular resuscitation
Support mitochondrial function
Components fully eliminated from the body
Suitable for administration by a wide range of medical personnel
No behavioral or physical post-resuscitation impairment
Maintain or restore normal species dependent values for:
Electrolytes concentrations
Osmolarity
Tonicity
Colloid osmotic pressure
Viscosity
Acid-Base homeostasis
Caloric requirements

(12). Survival rate at 24 h were significantly higher when pigs were resuscitated from hemorrhagic shock with the PEG product, when compared to whole blood and hextend (100, 17, and 0%, respectively). The PEG solution also improved mean arterial pressure and capillary perfusion when compared to the other products.

Hypertonic saline is a product that has been heavily studied in brain injury resuscitation. Hypertonic saline (3.5–7%) has been enriched with adenosine, lidocaine, and magnesium. The use of this formula, named ALM therapy, also led to promising results in pre-clinical rodent and swine models. The solution extends survival, reduces ongoing hemorrhage, modulate coagulopathy, and prevents immunodeficiency (13). Encouraging benefits have been observed in rodent models of traumatic brain injury with increased survival, cardiac function, and cortical blood flow (14). Conversely, in pigs receiving lipopolysaccharide, ALM therapy led to a reversible hypotensive and hypometabolic state, with reduced markers of inflammation (15). This exemplifies that a given product is likely to be beneficial in specific shock scenarios. There is a paucity of data explaining the actual mechanism of action of the drug; modulation of damage-associated molecular pathways and reduction in the inflammasome (Multiprotein complex that activates the pro-inflammatory cytokines interleukin 1b and 18) activity might contribute to clinical effects (16).

NOVEL BLOOD PRODUCTS/BLOOD PRODUCT REPLACEMENT

Current evidence strongly supports using blood products over crystalloids or synthetic colloids to treat human patients with hemorrhagic shock in both civilian and military patients. There is ample evidence showing the deleterious effects of over resuscitation with isotonic crystalloids associated with edema, cellular, metabolic, and immune dysfunction (17). Analysis of military casualties has shown that the use of blood in the treatment of combat casualties has saved lives. In a recent report, investigators estimated that 873 additional service members would have died in the wars in Iraq and Afghanistan had they not received blood products for their traumatic injuries (18). The clinical benefits of blood conflict with their use: they come in limited supply or might be unavailable altogether in combat, are complicated to store, have a limited shelf life, and can be associated with bacterial contamination (19, 20). The development of field-expedient blood products or substitutes is a primary focus for the military community. Synthetic products allow control of the supply chain while avoiding the risk of transferring disease from blood donor to the recipient.

Red Blood Cells Replacement Products

The development of hemoglobin-based oxygen carriers (HBOC) has been a dynamic field for decades. Numerous products showed promises in animal models but unfortunately were not successful in human clinical trials. A single meta-analysis, which has since been criticized (21–23), cast serious doubt on the clinical benefits of HBOC while outlining a high incidence of complications (24). Therefore, there is currently no FDA-approved HBOC in clinical use in human or veterinary medicine. Lack of clinical benefit has been attributed to nitric oxide-scavenging properties of hemoglobin leading to hypertension, oxygen oversupply, heme-mediated oxidative stress (25–27). Another limitation of earlier HBOC was the lack of dynamic oxygen affinity. In health, the hemoglobin saturation curve is sigmoid due to its allosteric effector 2,3-Diphosphoglycerate (2,3-DPG) and collaborative binding of oxygen (i.e., cooperativity: binding of the first oxygen molecule facilitates the binding of the next one, etc.). First-generation HBOC did not present such properties (28). Common side effects reported after using a wide range of HBOC products include gastrointestinal symptoms, pancreatic and liver enzyme elevation, myocardial infarction, arrhythmias, renal injury, and death (29).

While clinical complications were outlined, this meta-analysis also provided the industry with guidance to improve future products. Refinement involved chemical alterations to prolong half-lives such as polymerization or linking to non-protein molecules such as PEG or polyoxyethylene. HBOCs can be administered with antioxidant molecules, such as ascorbic acid, to prevent oxidative stress (30). Cross-linking with antioxidant enzymes, such as superoxide dismutase or catalase, has also been investigated in a rat model of severe cerebral ischemia-reperfusion showing improved perfusion and injury mitigation (31).

A PEGylated carboxyhemoglobin compound (Sanguinate™) is in clinical development. PEGylation prolongs circulating half-life by interfering with cell surface receptors involved in removal from circulation, prevents extravasation by increasing molecular weight, and reduces immunogenicity. Carboxylation prevents the formation of methemoglobin during storage. This molecule also releases carbon monoxide; while at high concentration, carbon monoxide is toxic, at lower concentrations, it protects cells from ischemia by mitigating inflammation, oxidative stress, and apoptosis (32). In rats subjected to hemorrhagic shock, PEGylated carboxyhemoglobin reduced evidence of renal injury (tubular histologic damage as well as neutrophil gelatinase-associated lipocalin and tumor necrosis factor alpha immunohistochemistry) despite not improving renal tissue oxygenation (33). In another study, PEGylated carboxyhemoglobin resulted in less volume requirement and prolonged survival when compared to synthetic colloids (6% hetastarch) (34). In a rat model of LPS-induced shock, animals receiving an isotonic crystalloid and the carboxyhemoglobin compound showed improvement in renal cortical microcirculatory partial pressure in oxygen as well as intravital microscopy markers of improved skeletal muscle microcirculation, when compared to those receiving the isotonic crystalloid alone. The addition of norepinephrine did not further enhance cortical oxygen delivery. While there was no difference across groups in biomarkers of renal injury, the carboxyhemoglobin did not improve immunohistological markers of renal injury (35).

PEGylated carboxyhemoglobin has been further coupled with polynitroxyl. This chemical modification leverages the benefits of carboxylation, as discussed above, while providing superoxide

dismutase and catalase-like activities. This modification affords antioxidant properties. This molecule was recently investigated in a guinea pig model of combined traumatic brain injury and hemorrhagic shock, which are the most lethal injuries in military casualties (36). Administration of this hyperoncotic solution following controlled cortical impact and hemorrhagic shock improved perfusion and reduced neuronal injury compared to lactated Ringer's.

Hemopure® (or HBOC-201) is another promising HBOC. It is a glutaraldehyde-polymerized, bovine hemoglobin. This compound has been studied in large animals for selective aortic arch perfusion (SAAP), an advanced endovascular resuscitation technique combining aortic balloon occlusion and proximal perfusion. In combination with SAAP, this HBOC was associated with successful outcomes following traumatic cardiac arrest modeled in pigs (37, 38). Such approach will potentially allow for prompt, blood-free augmentation in arterial oxygen content following traumatic exsanguination in the prehospital settings.

Side effects associated with first-generation HBOC have in part been attributed to their small molecular size (39). Another product refinement effort, therefore, focuses on developing products made up of large molecular weight hemoglobin polymers. Larger HBOCs reduce extravasation and renal injury, as well as nitric oxide scavenging. Those benefits materialized in a rat study of hemorrhagic shock, where large polymerized bovine hemoglobin restored blood pressure and cardiac function similar to fresh whole blood. Stored whole blood, however, was associated with renal and hepatic injury (40). The effects of those products on coagulation have yet to be determined. For instance, Polyheme®, a now-discontinued product, enhanced fibrinolysis (41), which is already a concern in trauma patients. There is, therefore, a concern that hyperfibrinolysis might be a property shared across various HBOCs.

Another product under development leverages a heme-based protein found in the thermostable bacterium *Thermoanaerobacter tengcongensis*. This molecule has a higher affinity for oxygen than hemoglobin, which allows for preferential delivery to hypoxic tissue. It also has a lower affinity for nitric oxide, which theoretically will not present the same hypertensive complications observed with first-generation HBOC. Similar to other blood product substitutes, the molecule is polymerized and PEGylated to prolong half-life (42). Being smaller than a red blood cell, the compound travels more easily through the microcirculation. In an ovine model of myocardial injury, administration of Omniox® resulted in improved myocardial oxygenation and contractility compared to control (42).

Another compound derived from the lugworm (*Arenicola marina*) is also penetrating the market as a preservation solution for organ transplants. The molecule is a large hemoglobin molecule that spontaneously occurs in the polychaete. It can load 156 oxygen molecules for transport, which is much higher than the four molecules the mammalian hemoglobin carries (43). The molecule, when administered to rats subjected to controlled cortical impact, improved blood pressure and, importantly, improved brain tissue oxygenation transiently (44). If further studies continue to show similar success, this compound might provide a bridging tool for patients with traumatic brain injury in the prehospital setting.

Hemoglobin can also be encapsulated to delay removal from circulation (45). The encapsulation process protects the molecules from degradation and oxidation while allowing for oxygen movement across the membrane. Much remains to be done to evaluate the immunogenicity of individual constructs. However, chronic administration of one of these encapsulated compounds to rats did not lead to significant antibody formation or tissue injury (46). The hemoglobin molecule can also be encapsulated with other molecules that preserve its structure and function (carbonic anhydrase, antioxidant enzymes, methemoglobin reductase, 2,3 DPG) (47). One such example is the bioparticle Erythromer®. Human hemoglobin is encapsulated in a membrane with compounds to lower oxygen affinity, prevent oxidation and prolong half-life. The bioparticle remains smaller than a red blood cell, thereby allowing it to navigate more easily through the microcirculation. The product also has the potential to be freeze-dried. In the lung, due to the higher pH, a novel compound bound to the inner membrane of the construct simulates 2,3 DPG activity. When the pH decreases, the novel compound interacts with hemoglobin and facilitates oxygen release. This facilitated release promotes oxygen delivery to hypoxic tissues.

In vitro production of red blood cells has been another approach to overcoming short supplies in red blood cells (48, 49). Farmed red blood cells development will free blood banks from concerns arising from donor-induced contamination of blood products and would provide a sustainable source of red blood cells if scaled appropriately. The ideal farmed red blood cell should be universally compatible and lead to no immunologic reaction. Most research efforts in the field have been funded by the Defense Advanced Research Projects Agency and leverage human stem cells to grow cultured red blood cells.

Research focusing on non-hemoglobin-based oxygen transport has been a dynamic field owing to earlier complications associated with HBOC as well as intrinsic limitations of hemoglobin-derived substitutes. Of those, perfluorocarbons (PFC) have been heavily studied. PFCs are amphipathic molecules; they transport oxygen with a weaker bond than hemoglobin, which leads to a linear oxygen saturation curve rather than a sigmoidal curve. While this translates to the need for higher partial pressure in oxygen for similar oxygen loading, oxygen unloading to tissue is better. Once in emulsion, those molecules can circulate through the microcirculation more efficiently than red blood cells owing to their smaller size. Similar to many HBOCs, several PFCs compounds have failed to translate from bench to bedside, but research and development efforts are still ongoing. Recent hemorrhagic shock studies in swine failed to show a benefit of a newer molecule (dodecafluoropentane) co-administered with fresh frozen plasma when compared to whole blood (50).

Iron-containing porphyrins have also been studied but do not currently seem to be an active area of product development. A porphyrin molecule can be combined with an iron atom to replicate the heme molecule (51). This molecule has then been encapsulated into a PEGylated lipid bilayer (52).

Novel Platelet Products

Platelets are certainly the most challenging blood product to collect, process, ship, and store. Furthermore, they are expensive, have a short shelf life (5–14 days), and carry a higher risk of transfusion complications than other blood products such as packed RBC and plasma (53). In human medicine, platelets comprise only 10% of blood transfusion yet results in 25% of the transfusion reactions (54). Platelet transfusions are occasionally needed in times of severe thrombocytopenia due to immune-mediated conditions, neoplasia, bone marrow suppression and disseminated intravascular coagulopathy (55). Additionally, in people, platelet transfusions have been recommended as part of a balanced hemostatic resuscitation strategy for individuals who have sustained severe trauma and blood loss (56). However, transfusion of canine platelets is uncommon in veterinary medicine due to the high cost, decreased availability, and short shelf life (typically 5–7 days at room temperature) of fresh platelets (57).

Artificial platelets will address some of these challenges. SynthoPlate® is made of liposomes that are "decorated" with multiple types of peptides on their surface. One peptide is a von Willebrand factor binding peptide, which facilitates adherence to circulating or tethered von Willebrand factor. Another peptide is a collagen-binding peptide allowing the liposome to adhere to exposed collagen. The third peptide is GP IIb-IIIa binding fibrinogen-mimetic peptide allowing the liposome to participate in aggregation with other platelets (58). SynthoPlate® is not designed to replicate all of the capabilities of natural platelets such as degranulation, contraction, and morphologic changes. However, SynthoPlate® can help active platelets adhere to surfaces as well as allow multiple platelets to bind to them, acting as an extender for the host platelets (59).

SynthoPlate® has shown promise in several animal studies. Early studies showed that a mixture of aggregation and adhesions peptides reduced tail vein bleeding time in mice compared to liposomes decorated with only one type of peptide or saline (59). Another interesting study examined the effect of SynthoPlate® in thrombocytopenic mice. In this study, the investigators showed that SynthoPlate® administered to thrombocytopenic mice reduced bleeding time in a dose-dependent fashion. Even more interesting, at the highest dose of SynthoPlate® administered, bleeding times in these mice returned to near control levels suggesting that SynthoPlate® can potentially control bleeding even in animals with very low levels of natural platelets (60). In a model of uncontrolled hemorrhage, mice were administered SynthoPlate® either before or after liver injury. Under both conditions, SynthoPlate® administration resulted in significantly decreased blood loss compared to animals that did not receive SynthoPlate® (61). Finally, a large animal model showed similar results. In this model, pigs with a femoral artery injury were administered a bolus of SynthoPlate® as part of a resuscitation strategy. Not only was bleeding reduced in the pigs administered SynthoPlate® but the authors also reported an improved survival. In the SynthoPlate® group there was 100% survival after 60 min and 75% survival after 90 min, while the control group showed a 25% survival after 60 min and 0% survival after 90 min (58).

Synthetic platelet products offer several benefits over natural and modified platelets. They are shelf stable at room temperature and are expected to have a robust shelf life. They can be produced in large quantities once manufacturing has been optimized. Cryopreserved and lyophilized platelet products need to be harvested from donors and then processed, which could affect the availability of the finished products. Additionally, all platelet products derived from donors carry some risk of transfusion reaction, although the incidence of transfusion reactions secondary to platelet administration in veterinary medicine is not well established (55, 57). Perhaps the most attractive aspect of these synthetic platelet products for veterinary professionals is that they are expected to have little antigenicity and have already proven to work in several species without significant immunologic reactions. This could provide veterinarians the ability to treat many species with platelet-like products that have not been available previously.

While this product is early in its development and studies have yet to be performed in small animals, there are numerous potential clinical indications for synthetic platelets in veterinary medicine particularly in resource-constrained practices. Synthetic platelets are not a substitute for live platelets; however, they can be made economically and are not immunogenic (as expected). They may provide a way for general practitioners and specialists to treat immune mediated thrombocytopenia, consumptive coagulopathies, and bone marrow suppression, among other conditions. Treating feline patients, where no licensed platelet products for this species exist and fresh feline platelet products are not routinely available, might be of particular interest. These synthetic platelets may be able to extend the effect of the remaining platelets in animals preventing a bleeding diathesis while clinicians treat the underlying disease.

Naturally occurring platelet-derived hemostatic agents have also been evaluated as a replacement for current platelet products. Extracellular vesicles are small (10–1,000 nm diameter; exosomes 50–100 nm; microvesicles 100–1,000 nm) particles that express similar surface proteins as the cells they are secreted from. They contain a broad range of mediators and are capable of interacting with other cells and transferring their content to a target-cell. Platelet-derived extracellular vesicles isolated from leukoreduced apheresis platelets had endothelium-sparing properties and stimulated whole blood aggregation. Those vesicles reduced blood loss in a mouse model of uncontrolled blood loss (62).

Freeze-Dried/Lyophilized Platelets

The introduction of lyophilized platelets (LP) has been a promising development in platelet substitutes. Lyophilized canine platelets (StablePlate®) is an FDA-approved and commercially available product that may simplify and increase platelet administration to veterinary patients. These LPs are made by obtaining leukoreduced apheresis platelets from donor dogs. These platelets are stabilized with trehalose, a disaccharide found in organisms able to withstand intense dehydration, mixed with a buffering solution and lyophilized (63, 64). This process allows the LPs to be room stable for

up to 12 months and can be rapidly reconstituted with sterile water. This product is licensed for use in thrombocytopenic dogs with uncontrolled bleeding. A similar human-derived product dubbed Thrombosomes® is currently being investigated for use in people (65). A similar product called Stasix has also been developed was used in a swine liver injury model. In this experiment, pigs underwent a liver injury and were treated with either a low dose of Stasix or saline. Eighty percentage of the pigs treated with Stasix survived while only 20% survived in the saline treated group. However, pathologic thrombi were noted in the Stasix treated group, suggesting there may be some safety concerns with this product (66).

In 2017, investigators reported on the safety of canine LPs in a coronary bypass canine model. The group performed coronary bypass on eight dogs and returned up to 33% of their circulating platelet count with LPs. The group reported normal coagulation parameters and no abnormal thrombus formation in these dogs (67). More recently, Goggs et al. performed a multicenter randomized clinical trial of LP vs. dimethyl sulfoxide stabilized cryopreserved canine platelets for severely thrombocytopenic dogs (68). The group found that at 1 h after infusion the LP group had lower bleeding scores than the cryopreserved platelet group, but there was no significant difference at 24 h between groups. Furthermore, there was no difference between groups in platelet count change, need for additional red blood cell transfusions or survival to discharge. Studies are ongoing investigating the utility of canine LP for use in hemorrhagic shock and trauma.

Fresh-Frozen Plasma Replacement Products

The development of an FDA-approved freeze-dried plasma (FDP) has been a priority for the Department of Defense. Current candidates include single-donor or pooled products. Heterogeneity in plasma hemostatic properties between donors is compensated for by pooling, thereby homogenizing clinical efficacy. Plasma can be purified by leukoreduction, solvent/detergent treatment, or microfiltration to obtain a product void of cells or cell debris. It can then be freeze-dried-lyophilized through a combination of low temperature, low pressure and low moisture circulating air or it can be spray dried by aerosolizing it into a high-temperature chamber to remove the moisture (69). FDP has regained prominence for trauma resuscitation in people. Three different countries are now manufacturing FDP for people (70), and it has been used with great success on the battlefield during the recent conflicts (71, 72). Beyond its use on the battlefield, FDP has shown to be efficacious in use for civilian traumas. In a study of aeromedical evacuation civilian trauma patients in the United Kingdom, patients transfused with FDP prehospital had a decreased need for red cell transfusions and decreased time to administration of blood products (73). FDP offers numerous advantages over FFP. FDP is shelf-stable at room temperatures and can be quickly reconstituted in $<$5 min with sterile water. FDP is currently recommended by the Department of Defense to resuscitate individuals in hemorrhagic shock when whole blood is not available or as part of a balanced resuscitation strategy (1 pRBC: 1 plasma: 1 platelets).

Currently, two companies have produced canine FDP with the help of Department of Defense funding. Bodevet Inc. has produced a pooled plasma product dubbed StablePlas®, which is expected to be FDA cleared and commercially available soon. Another company, Mantel Technologies, is also producing a high-quality canine FDP product. Both products can be manufactured in a plasma bag, can be reconstituted in under 5 min with sterile water, and have a long shelf life at room temperature. In a recent study, both products were considered to have hemostatic properties equivalent to canine fresh frozen plasma and in general retained their hemostatic capacity for up to 14 days after reconstitution when refrigerated (74). DoD funded studies are ongoing evaluating the *in vivo* use of canine FDP in hemorrhagic shock and trauma.

Resuscitation Adjuncts

Regardless of the qualities of a novel fluid, there is also a growing interest in non-fluid-based resuscitation adjuncts for patients with hemorrhagic shock. Resuscitative endovascular balloon occlusion (or REBOA) is an endovascular hemorrhage control tool whereby a balloon-tipped catheter is inserted in the aorta (75). The balloon can be inflated in various locations of the aorta depending on the source of bleeding. Aortic occlusion can be complete, partial (allowing limited flow, continuously, around the balloon), or intermittent (the balloon is completely inflated and completely deflated at fixed intervals or after a set hypotension threshold is reached). REBOA is a bridging therapy that allows rapid stabilization of the patient until definitive care. However, it creates a severe ischemia-reperfusion syndrome for which the fluids of the future might be important and especially relevant. Other similar resuscitation tools that will be improved with new generation fluids include SAAP and extracorporeal membrane oxygenation.

LIMITATIONS

Reviewing the literature to discuss fluids of the future outlines that much remains to be done to have a product with proven benefits in veterinary patients and that also overcame regulatory evaluation to make it to market. Synthetic platelets are the most likely product to become available to veterinary researchers to validate their efficacy in various clinical scenarios since they are FDA approved. The gap between bench to bedside is a major limitation for several of those products as many will not prove efficacious in our patients. This is the main focus of translational research. Animal data, especially in dogs and pigs, is the basis for translation into veterinary and human clinical practice. Many of the observed benefits of the products reviewed here might disappear in clinical studies. Veterinarians, physicians, bioengineers should strive to collaborate to ultimately evaluate those products to ultimately improve patient outcome. Such success will likely be the result of

partnership between military agencies, civilian researchers, and private companies.

CONCLUSIONS

Fluids are unquestionably an important part of resuscitation from several states of shock. Clinical and laboratory research have outlined several limitations of currently available products, which motivates efforts to develop new-generation fluids that will hopefully overcome those limitations. The search for the ideal fluid is driven by military research owing to specific operational constraints. Those efforts are also paralleled and supported by civilian efforts. Altogether, those research and development initiatives are likely to benefit both civilian and military veterinary patients. There are several candidates covering a wide range of syndromes, many of those remain early in the spectrum of translation from laboratory research to clinical use.

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GH and TE: manuscript drafting and editing. All authors contributed to the article and approved the submitted version.

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Closed-Loop Control for Fluid Resuscitation: Recent Advances and Future Challenges

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Fluid therapy is extensively used to treat traumatized patients as well as patients during surgery. The fluid therapy process is complex due to interpatient variability in response to therapy as well as other complicating factors such as comorbidities and general anesthesia. These complexities can result in under- or over-resuscitation. Given the complexity of the fluid management process as well as the increased capabilities in hemodynamic monitoring, closed-loop fluid management can reduce the workload of the overworked clinician while ensuring specific constraints on hemodynamic endpoints are met with higher accuracy. The goal of this paper is to provide an overview of closed-loop control systems for fluid management and highlight several key steps in transitioning such a technology from bench to the bedside.

Keywords: closed-loop control, fluid management, large-volume resuscitation, goal-directed therapy, hemorrhage, hypotension

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INTRODUCTION

Fluid therapy is used extensively to treat traumatized patients as well as patients during surgery (1, 2). Fluid therapy is a challenging process involving the consideration of interpatient and intrapatient variability in response to therapy as well as other factors such as comorbidities and general anesthesia. These complexities can result in under- or over-resuscitation (3–5). Given the complexity of the fluid management process, as well as the increased capabilities in hemodynamic monitoring, closed-loop fluid management can reduce the workload of the overworked clinician while ensuring specific constraints on hemodynamic endpoints are met with higher accuracy.

One industry that has witnessed a wide adoption of active (i.e., closed-loop) control technologies is the aerospace industry, where closed-loop control technologies (the *autopilot*) have been used in various aircrafts over the past several decades. More recently, advances in autonomous driving holds the promise of using closed-loop technologies for the driverless operation of vehicles in the near future. Although closed-loop control technologies have been used in various industries for many years, it is not until recently that active control technology has transitioned into medical applications with the majority of applications focusing on pre-clinical or research settings.

WHAT IS A CLOSED-LOOP CONTROL SYSTEM?

In many systems related problems, a specific variable of interest (the controlled variable) needs to be maintained at a desired value. For example, in the classical inverted pendulum control problem

consisting of a pendulum and a moving cart, the goal is to maintain the pendulum in a vertical position by moving the cart horizontally. Every closed-loop control system has three components; namely, (i) a *sensor*, that measures a relevant variable of interest (e.g., the angle of the pendulum relative to the vertical position); (ii) an *actuator* (e.g., electric motor on the cart), that changes the state of the system in order to drive the controlled variable of interest to a desired value; and (iii) a *controller* or *processor*, that uses the sensor measurements in order to compute an appropriate action that drives the actuator to execute the desired control action. The controller can be considered the central processing unit of the system (the "brain") and, in general, is implemented using proprietary software on a computing device. The general architecture of a closed-loop control system is shown in **Figure 1**.

Using this architecture, it is straightforward to apply this process to a clinical problem such as fluid management. In this case, the goal would be to maintain the controlled variable of interest at a desired value (e.g., maintaining the cardiac index at 3 L/min/m^2). In order to design a feedback control system, we need a sensor (e.g., a hemodynamic monitor and its associated sensor to measure cardiac output) and an actuator (e.g., an infusion pump to administer IV fluids) to regulate the trajectory of the controlled variable of interest over time. The control system can be implemented on a computing device such as a computer or a small and limited-resource computing device such as a microcontroller.

An important property of a closed-loop system is system stability. Specifically, closed-loop system stability ensures that system state variables do not significantly deviate from their desired set point values over time. For example, if a developed control system for controlling an inverted pendulum is appropriately designed and the closed-loop system is stable, then we are guaranteed that, for all initial angular positions and velocities relative to the vertical plane, the controlled system will maintain the pendulum at the desired 90-degree angle with respect to the horizontal position of the cart.

Closed-loop stability is an extremely important property for a controlled system. Instability may result in *actuator saturation* (e.g., fluid infusion amplitudes and rates attaining their maximum limits) as well as oscillatory system behavior or, in the worst case, divergent trajectories of the controlled variables. Lyapunov stability theory provides a powerful framework for guaranteeing system stability. Using this framework, an "energy-like" Lyapunov function is constructed and shown that its rate of change with respect to time is negative reflecting the fact that the "energy" of the closed-loop (i.e., controlled) system is decreasing over time (6). An intuitive example of a stable system is a marble placed in a bowl, where, no matter where you release the marble from within the bowl, the marble converges to the point of minimum potential (i.e., energy) corresponding to the bottom point of the bowl (i.e., equilibrium point) after dissipating its kinetic energy.

CLOSED-LOOP CONTROL IN BIOMEDICINE

Although closed-loop systems in biomedicine, including closed-loop drug delivery systems (7), have been designed and investigated as part of research initiatives, a renewed interest in active control has resulted in the development of a number of commercial medical products based on closed-loop control technologies. One notable example is the artificial pancreas, where continuous blood glucose measurements are used to automatically guide the administration of insulin using a computer-controlled insulin pump (8).

The renewed interest in closed-loop technologies for improving performance in clinical applications is due to multiple factors. Until recently, control system designs in biomedicine have been largely based on heuristics (i.e., trial-and-error-based methods). This is due to the complexities inherent in system physiology, wherein mathematical models capturing complex physiological mechanisms of action are not readily developed. Although there has been considerable progress in understanding the pharmacokinetics and pharmacodynamics of drug distribution and drug effect using compartmental models in pharmacology (9), the distribution of fluids using compartmental and volume kinetic models (10–12), and lumped parameter models of blood volume response to fluid infusion (13), such models are approximations to the actual patient physiology. The gap between system modeling and the actual system physiology has been the main limiting factor in the use of rigorous control design frameworks that have been widely used in, for example, the aerospace industry. This is due to the fact that, unlike human or animal physiology, aircraft system dynamics are governed by the well-established laws of aerodynamics and mechanics.

Compartmental models, which are characterized by conservation laws (e.g., conservation of mass, energy, and fluid) involve several simplifying assumptions. One important assumption is that the drug or fluid distribution in the body can be approximated by using only a few *compartments*. A compartment is a macroscopic subsystem involving kinetic homogeneity, where it is assumed that any material entering the compartment is instantaneously mixed with the material in that compartment. Compartmental models have been successfully used to provide approximate models for capturing the behavior of drug and fluid distribution in the body. In addition, such models provide an opportunity for the use of *model-based control design* approaches that use mathematically rigorous closed-loop control techniques to solve specific problems related to drug and fluid distribution management.

Although compartmental models provide the opportunity to leverage model-based control designs, a critical limitation of this design approach is that the patient-specific parameters that define these models are vaguely known. More specifically, compartmental models capture the approximate physiological *structure* of the biomedical system being modeled, whereas the model parameter values (e.g., transfer coefficients between different compartments) are uncertain and vary from patient to

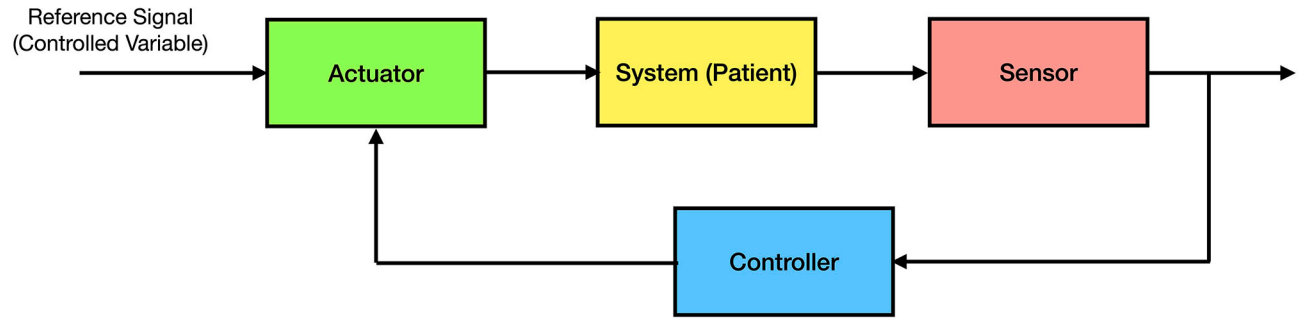

FIGURE 1 | General architecture of a closed-loop control system.

patient; these model parameter values are critical in being able to design effective closed-loop, model-based control systems.

Given the aforementioned complexities associated with model-based controller designs for biomedical systems, heuristic approaches have been the dominant control design methods used for controlling these systems. In particular, specific controller design parameters (e.g., the gains of a *proportional-integral-derivative* controller, also known as a PID controller) are "tuned" based on experimental data (14). In this approach, the system physiology is effectively modeled as a "black box," and the control system parameters are designed (i.e., tuned) by trial and error.

An inherent assumption of heuristic control design methods is that the available data obtained through animal studies (14, 15) or patient population data (16–18) is representative of *all* patients. This approach may be useful when dealing with a problem where a limited understanding of the dynamics or the process to be controlled exists. However, it is predicated on the overly restrictive assumption that all patients are modeled as an "average patient." Creating an average patient model based on statistical data or limited experimental data has the potential to negatively impact the performance and stability of the closed-loop system when applied to an actual patient.

There have been a number of recent advances that have created an optimal platform for transitioning closed-loop control technologies into a clinical setting. From a theoretical perspective, recent developments in control theory, and specifically, *robust* and *adaptive control*, have allowed for a rigorous control system design of uncertain systems, wherein only an *approximate* system model is used to capture the system physiology and the system parameter values (which are unique to each individual patient) are assumed to lie between upper and lower bounds or are unknown and estimated in real-time. Within this context, compartmental models that capture general fluid or drug distribution can be used to guide the control system design. Examples include using adaptive control technologies to deliver general anesthesia (19, 20) and, more recently, closed-loop control for fluid resuscitation (21).

A second factor that has facilitated the development of advanced closed-loop control technologies is the improved computational power and miniaturization of computer chips. Real-time computation of complex control laws requiring the solution of multiple ordinary differential equations and matrix computations in real-time [e.g., for closed-loop control of fluid resuscitation (21)] on a small computing device was not possible until recently.

Finally, the development of mechanistic models linking the dynamics between biological and physiological laws leading to improved understanding of system physiology (22) and the new paradigm of *in silico* testing and *hardware-in-the-loop simulations* have accelerated the development of closed-loop system design in biomedicine (23). As opposed to testing the design of the control system on animals, which is costly and labor intensive, a mathematical model of the patient can be simulated and the performance of the controller can be tested using *in silico* testing. Specifically, there has been recent interest by the FDA to further leverage the promise of *in silico* models in closed-loop controlled device development (24, 25). The fidelity of *in silico* models have progressed to a level where the FDA recently approved the use of *in silico* testing as a replacement of animal studies prior to testing of an artificial pancreas in humans (26).

CLOSED-LOOP CONTROL FOR FLUID RESUSCITATION

Closed-loop control for fluid resuscitation has been investigated by several research groups. Specifically, closed-loop (i.e., fully automated) and semi-automated fluid management for burn patients has been extensively studied by researchers at the US Army Institute of Surgical Research, San Antonio, TX (27, 28). The semi-automated implementation of this work was later commercialized as part of a clinical decision support tool for fluid management of burn patients. The developed framework, which used urine output rates as the controlled variable of interest, employed a heuristics-based non-linear relationship between the urine output rate and the fluid infusion rate to guide the resuscitation process. A clinical study involving 39 acute burn patients with >20% total body surface area, showed that the developed clinical decision support system reduced the total amount of fluid administered. In addition, a larger number of patients resuscitated by the clinical decision support system met the hourly urine output goals set by the study team.

The authors in (14) investigated the use of their closed-loop control system to guide fluid resuscitation for burn shock in sheep. Specifically, the performance of a PID controller was compared with manual resuscitation when using the urine output rate as the feedback control signal. It was shown that the PID controller was able to produce urine output rates within the desired range with less variation as compared to manual resuscitation. Various controllers based on heuristic design methods such as PID, fuzzy logic, and decision tables have been tested and reviewed elsewhere (29) including studies involving the co-administration of vasopressor and fluids using a closed-loop architecture (30–32).

Another series of recent studies have investigated the use of closed-loop control for goal directed fluid therapy. Specifically, hemodynamic data obtained from patients has been used to develop an algorithm to administer a bolus of fluid (33). The performance of the approach in hemorrhaged pigs was evaluated by comparing the closed-loop system's response to volume depletion with manual fluid resuscitation by anesthesiologists. The study demonstrated that the closed-loop fluid administration system responded appropriately and produced a higher cardiac index as compared to the group which received manual fluid resuscitation by anesthesiologists. The same algorithm was later used as part of a pilot study in humans (18).

While the majority of currently designed closed-loop systems use heuristic approaches to determine fluid administration rates and volumes, a notable exception has been the employment of an adaptive control system predicated on a compartmental model to resuscitate dogs subject to absolute and relative hypovolemia (21). The study involved a total of nine experiments on five dogs of different weights experiencing controlled or uncontrolled hemorrhage as well as cases involving relative and absolute hypovolemia. In this pilot study, it was shown that the adaptive control system could successfully drive stroke volume variation to a predetermined value set by the clinician.

In a recent work, authors in (34) investigate a model-based controller design predicated on a lumped parameter model of blood volume response involving three parameters (13). Specifically, this closed-loop control framework involves a two-step process: a "calibration" phase involving administering an initial fluid bolus and observing the patient's response followed by using a model reference adaptive control architecture to guide fluid infusion. However, as discussed by the authors, the performance of this framework beyond *in silico* tests for 30 randomly generated patients was not investigated. It is also unclear whether the proposed architecture is robust to unmodeled dynamics not captured by the lumped parameter model.

DISCUSSION

Given the complexity of individual patient physiology under various clinical scenarios and issues associated with under- or over-resuscitation (3–5), designing a closed-loop control system for fluid resuscitation needs to involve a collaborative team effort between control engineers and clinicians. The control system design process needs to employ rigorous control engineering frameworks to address important issues such as system performance, stability, and robustness to modeling uncertainly as well as disturbances (e.g., how the system will respond to rapid changes in patient physiology). Leveraging decades of knowledge gained from physiological modeling, including compartmental models and volume kinetics (10–12), holds a great promise for developing feedback control technologies that will permit a transition from the bench to the bedside.

Clinical insight is critical in designing closed-loop systems for fluid management. The controlled system needs to administer fluids when appropriate, and needs to stop fluid administration when key physiological endpoints are maintained. In the case where the anticipated response to fluid administration is not achieved by the closed-loop system, the system needs to alert the clinician to take over the fluid administration (i.e., control) in much the same way wherein a well-designed autopilot alerts the pilot to take over control of an aircraft.

Prior to transitioning a closed-loop control system for fluid management to a clinical setting, such system needs to be comprehensively tested. This will involve a series of tests ranging from *in silico* testing and hardware-in-the-loop simulation to pre-clinical and clinical testing. In addition, such tests need to assess the system performance in complex clinical scenarios to ensure safety and effectiveness. The clinical and workflow impact of using a closed-loop control system for fluid management in a clinical setting needs to be investigated in future studies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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